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ON CERTAIN TONIC OR POSTURAL REFLEXES IN HEMIPLEGIA, WITH SPECIAL REFERENCE TO THE SO-CALLED "ASSOCIATED MOVEMENTS."[1]

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Chapter I.—Introduction.

In earlier papers the writer has endeavoured to analyse in physiological terms the spasticity resulting from pyramidal system lesions and also the reflex movements in the lower limbs in the two clinical forms of paraplegia, the extended and the flexed [15] [16]. These phenomena were identified with certain tonic and phasic reflex reactions described by Sherrington. A similar detailed analysis of the familiar associated movements of the paralysed limbs in hemiplegia remains to be undertaken on the same lines. In the papers referred to above some preliminary considerations on the subject were stated. Thus, these movements were described as tonic or postural reactions, that is, as reflex variations in muscle tone, rather than as movements in the strict physiological sense. This conclusion was based upon the following considerations.

Neurologists are learning from Sherrington to regard muscle tone as the basis of posture, and decerebrate rigidity as a form of reflex standing. In the earlier analysis of spasticity, as it occurs in hemiplegia and in the extended form of spastic paraplegia, reasons were given for regarding it as physiologically identical with experimentally produced decerebrate rigidity. It was pointed out that all voluntary purposive movements are accompanied by an appropriate postural adjustment of the rest of the skeletal musculature, and that in forceful movements this adjustment or adaptation is necessarily bilateral and widespread. Although carried out under voluntary control, postural adaptation is a function of reflex mechanisms situated in the brain-stem, which are not put out of action by the lesion which produces hemiplegia and abolishes voluntary control of the musculature on the affected side of the body. In these circumstances, we should still expect postural reactions to occur when forceful voluntary motor activities are carried out by the musculature of the sound half of the body. Now, however, deprived of cortical control, they would occur in exaggerated intensity and deprived of that fineness of adaptation which that control ensures. It was concluded that the "associated movements" of hemiplegia are phenomena of this order, appearing in the muscles of the affected side on certain voluntary movements of the normal limbs, or on such semi-voluntary movements as yawning. In other words, associated movements, or, as we shall call them, "associated reactions," are released postural reactions in muscles deprived of voluntary control.

With certain modifications in detail, this view as to the nature of

associated movements was reached by Riddoch and Buzzard [8]. The recent work of Magnus and his collaborators on the nervous regulation of posture in animals has indicated lines along which a further investigation may be carried out, and it is now proposed to record observations on such of the tonic reflexes described by Magnus as are to be found in man in cases of hemiplegia, and also to establish what relation, if any, there may be between these reflexes and the familiar associated reactions. Elsewhere [17] the present writer has given a résumé of the researches of Magnus and de Kleijn, to which the reader may be referred for more complete details than it is here possible to give. A short summary of the general nature and bearing of part of this work is, however, necessary at this point, so that the nomenclature adopted from time to time and the conclusions ultimately reached may be clear. In his experimental analysis of muscle tone, Sherrington showed that the tone of a given muscle is dependent upon the integrity of its afferent nerve supply. In addition, he observed that afferent impulses arising in the labyrinths and in the muscles and joints of the neck and limbs are capable of modifying, or of regulating, muscle tone. The researches of Magnus and his school have been devoted to the study of these regulating mechanisms and may now be said to have solved the main problems in the co-ordination of posture. Beginning with the decerebrate animal it was found that the otolith organs of the labyrinths (and not the semicircular canals) and the proprioceptors of the neck are the sources of impulses which by their influence on muscle tone produce reflexly a whole variety of attitudes of the limbs and trunk. Thus, changes in the position of the head (otoliths) in relation to the horizontal plane of space cause an identical variation in the extensor tonus of all four limbs. The maximal influence is exerted when the animal is inverted, and the minimal when the animal stands on its feet in a natural posture. Alterations in posture of the head in relation to the trunk also produce variations in limb tonus and therefore in attitude, quite apart from labyrinthine influences. Thus, rotation of the head to one side causes increase of extensor tonus in the limbs on the side to which the snout is directed, and diminution of extensor tone in the crossed limbs. Retraction of the head produces extensor spasm in the fore limbs and loss of extensor tone in the hind limbs, and ventral flexion of the head has the opposite result. In these circumstances the decerebrate animal can maintain a standing posture if it be carefully placed therein, and the variations in attitude described are not actively produced by reflex

movements of the head, but by the observer who uses the head as a species of handle and thus sets up the postural reactions described. Apart from this the head of the decerebrate animal is unalterably retracted, and does not possess the capacity of righting itself in space. Clearly, therefore, some of the postural mechanisms present in the nervous system of the intact animal have been removed in the process of decerebration, in which the brain-stem has been transected between pons and mid-brain. The study of the "mid-brain" preparation, an animal in which transection has been performed immediately cephalad to the mid-brain, reveals the localization of the remainder of the posture-regulating mechanism, for this preparation can not only stand, but can walk, run and jump, and can right itself no matter in what abnormal attitude the observer may place it. The sum total of the postural reflexes active in the decerebrate animal Magnus [5] speaks of as "standing reflexes," while the additional reflex reactions present in the "mid-brain" preparation, which enable the animal to maintain full reflex control of posture, he speaks of as "position" or "righting" reflexes ("Stellreflexe"). He has analysed these into five groups, according to their source and the muscles upon which they act. In apes, these five groups are: (1) optic (probably retinal) righting reflexes; (2) labyrinthine righting reflexes acting upon the head; (3) righting reflexes arising in the deep tissues of the body wall and regulating the position of the head; (4) righting reflexes arising in the deep structure of the neck and acting upon the trunk and limb muscles; and (5) righting reflexes arising in the deep tissues of the body wall and acting upon limb and trunk muscles.

It will be noted that Magnus does not record the existence of tonic reflexes (either "righting" reflexes, or "standing" reflexes) arising in the limb muscles and joints and acting on the limb muscles, though, as we have mentioned, Sherrington has found evidence of such reactions. [9]. As will appear later, it is to such a group that the associated reactions belong. In speaking of tonic reflexes arising in the labyrinths, we refer particularly to the otolith organs in the utricle and saccule, and not to the semicircular canals which play no part in the production of the tonic reflexes now under consideration. Further, it will be seen that the term "Stellreflexe" is here translated as "righting reflexes." This is clearly not a literal translation, which has been avoided as not conveying the full significance of this variety of tonic reaction. In a communication received by the present writer, Magnus has expressed the opinion that the translation adopted most adequately conveys his interpretation of the reflexes in question.

Chapter II.—Associated Reactions.

The so-called "associated movements" of hemiplegia which appear most characteristically in the limbs of the affected side are so familiar to neurologists that a detailed description of them is scarcely necessary. An admirable account of them has recently been given by Riddoch and Buzzard in a paper already referred to, in which these observers indicate how widespread these reactions may be, involving head, trunk and limb musculature. Such description of them as we shall give will be directed primarily to the elucidation of their nature and physiological significance, rather than to providing a general account.

The clinical material on which the present paper is based consists in the first place of a series of eighteen cases of hemiplegia studied during the years 1912-1914, when the reflex movements of the lower limbs were more particularly the object of study. The conclusions then reached have been briefly summarized in the introductory chapter, and have also been expressed in an earlier paper [16]. At that time the early papers of Magnus and de Kleijn were not accessible, and therefore no final analysis of associated reactions could well be carried out. Recently, however, a fresh series of twenty cases have been investigated and the whole subject re-surveyed in the light of our present knowledge of the nervous regulation of posture. Of the original series, five were cases of flaccid hemiplegia of recent origin, three due to vascular lesions in the region of the internal capsule, and two to cerebral compression by tumour. The present series consists of spastic hemiplegias with the usual signs of pyramidal tract involvement. This spasticity was of the familiar type, the arm being spastic in flexion and the leg in extension. In all but one the lesion was vascular in origin and presumably in the region of the internal capsule. The exception was a case of left-sided cerebral tumour, the exact localization of which yet awaits verification.

It may be observed that while we have compared the spasticity of hemiplegia with experimentally produced decerebrate rigidity, the localization of the lesion in the former case is not strictly comparable with that obtaining in the latter. It is not possible to enter into this question here, further than to refer the reader to a paper in which the present writer has reviewed the evidence in favour of the analogy between clinical and experimental states [18].

(1) *Conditions governing the occurrence of associated reactions.*—(*a*) In the reacting muscles of the hemiplegic side. In none of the

flaccid cases examined was any sign of an associated reaction in arm or leg detected. In the spastic cases, on the other hand, a more or less well-developed reaction on forceful voluntary activity of the normal limbs was constant. In two cases, indeed, no excursion of the paralysed arm occurred, but palpation revealed a distinct access of spasticity during the performance of the voluntary movement. We may say, therefore, that some degree of hypertonus in a case of hemiplegia is an essential preliminary to the development of an associated reaction. To this we may add that, in general, the higher the degree of spasticity present, the more forceful and the longer lasting will the associated reaction be. The force of the reaction cannot always be measured by the actual excursion of the limb. The most ample reactions of the kind were observed in a patient in whom spasticity was not very pronounced, but although of considerable amplitude they were not very forceful. The force of the reaction bears no relation to the degree of voluntary power retained by the affected limb, and in many instances far exceeds this and involves segments of the limb in which no voluntary activity remains—notably the forearm and hand.

(*b*) The nature of the voluntary activity necessary to invoke them. The form of voluntary muscular effort most effective in the production of associated reactions is forceful tonic contraction of muscles. No actual excursion of the parts acted upon by these muscles is essential. Thus a strong and maintained grasp of the normal hand is one of the most powerful stimuli for the reaction in the paralysed arm. Further, alternating movements, e.g., of the normal arm, when carried out rapidly and with a minimum of force do not commonly produce any associated reaction in the affected arm. However, a series of forceful punching movements of the normal arm does produce an associated response. Cutaneous stimuli, tactile or painful, have no effect, and the reflex movement that may result from such stimulation (Riddoch and Buzzard) bears no resemblance to the ordinary associated reaction now under discussion. In short, the adequate stimulus for an associated reaction in the muscles of the hemiplegic half of the body is strong tonic voluntary muscular contraction. Alternating movements are effective only when they are forceful and of a kind demanding widespread synergic fixation of the musculature. Even in these circumstances, the associated reaction is tonic and has no alternating character. Passive movements of the limbs have not been found effective in producing associated reactions.

We have chosen tonic voluntary activity of the normal limbs as the

type of stimulus most effective in eliciting an associated reaction, but it is not suggested that voluntary contraction of other muscles may not have a similar, if less pronounced, effect. Firm clenching of the jaws, stiffening of the neck muscles, and such quasi-involuntary activities as yawning and stretching and coughing, also produce associated reactions. Further, voluntary contraction of one of the limbs on the hemiplegic side may be productive of an associated reaction in the other. It is possible also that the elevation of the shoulder, abduction of the arm and flexion of the forearm, which may accompany the attempt of the patient voluntarily to extend his clenched fingers in the affected hand, may be of the nature of an associated reaction. In this case, however, as we shall see when discussing Marie and Foix's classification of "syncinésies," another type of movement may be in question. In every instance the voluntary contraction which constitutes the stimulus for an associated reaction, whether it be in the limb or trunk muscles, must be forceful and maintained.

(2) *The form of the associated reaction.*—As Riddoch and Buzzard have pointed out, the associated reaction may be very widespread, but it is with the limb reaction that we shall mainly deal, because this is more readily capable of accurate observation and recording than a tonic contraction in trunk muscles, and is therefore better adapted for the determination of the nature of associated reactions as a whole. As we shall see later, it is essential in studying associated reactions that the conditions of examination shall be constant. The following brief description applies to the reactions obtained from a patient lying on his back with the head in the median position. The normal arm lies extended and supported on the bed at the patient's side. The hand is then held by the observer and the patient commanded to give a strong, steady, and maintained grasp. No excursion of the arm occurs. In these circumstances the paralysed arm as it lies resting, semiflexed, across the patient's body, is seen to go into strong tonic contraction after a short interval. In this contraction every muscle of the limb and limb girdle may be both felt and seen to contract. In the majority of instances the flexors of the forearm are most affected, a slow movement of flexion at the elbow results, and the new posture taken up is maintained more or less steadily until the patient is told to relax the voluntary grasp. In addition to flexion of the elbow there is frequently some elevation of the shoulder and either adduction or abduction of the upper arm. In the former case the forearm and hand pass across the body towards the sound side, in the latter the forearm is lifted from

the body and moved away from the normal side. Practically always the fingers and wrist go into more pronounced flexion than was initially present, and the forearm rotates slightly towards the supinated position. The reaction in the paralysed leg is one of tonic extension with inversion and dorsiflexion of the foot and dorsiflexion of the hallux. Less frequently seen is extension at the elbow with full pronation of the forearm and some flexion of the hip, less of the knee and the dorsiflexor response of the foot and hallux already mentioned. Again, in some cases, the upper limb reaction may consist in general tonic rigidity with a movement entirely of adduction or of abduction of the upper arm. It has been said by earlier workers that for a given patient the reaction is invariable, but my observations do not altogether confirm this, for from time to time, the conditions remaining constant, flexion may be replaced by extension in the upper limb. If, however, the conditions are changed, then the associated reaction may undergo even more striking variations, which we shall discuss in a subsequent chapter.

(3) *Effect of form of voluntary movement on associated reaction.*—In many patients the form of the associated reaction does not vary according to that of the voluntary movement or posture eliciting it, and a stereotyped reaction is obtained, whether the voluntary activity be a powerful grasp with the arm extended, or tonic contraction of the limb flexors or extensors against the resistance exerted by the observer However, this is not always nor even generally the case, and the subjects examined differed widely in this respect. In one case tonic flexion and extension of the whole normal arm against resistance, and tonic activity of each segment of the limb separately and in both directions was tried, but in every test, whether the normal fingers were being extended against resistance or the elbow flexed, the same response was seen in the paralysed arm, namely, increased flexion at the elbow, abduction and elevation of the upper arm, slight supination of the forearm and increased flexion of wrist and digits. In other subjects, however, the form of the associated reaction could be completely modified according to the form of the voluntary movement of the sound arm. Thus voluntary flexion of the elbow against resistance evoked associated crossed flexion, while voluntary extension evoked ample associated extension (fig. 1).

Rarely, a given case may show a crossed associated reaction of opposite direction to the voluntary movement evoking it. Thus voluntary flexion is followed by associated extension and voluntary extension by flexion. This is true also of voluntary adduction and

abduction of the upper arm, although in this case a symmetrical response is no more commonly seen than one of opposite sense.

In one patient, the influence of reversing the form of the voluntary movement was less potent in modifying the associated reaction. Thus, voluntary flexion of the normal arm produced associated flexion, while

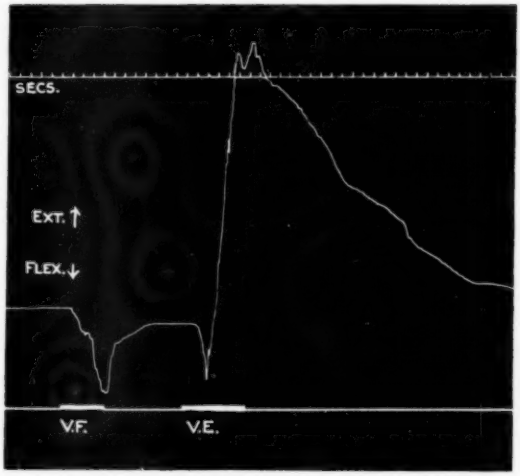


FIG. 1.

FIG. 2.

FIG. 1.—Inversion of form of associated reaction in hemiplegic arm on reversing form of voluntary movement. The voluntary activities were flexion of the normal against strong resistance followed by extension against resistance. Voluntary flexion (V.F. on signal record) is followed by associated flexion, and voluntary extension (V.E.) by associated extension. In the particular subject from whom this record was taken, the associated extension was commonly preceded by a transient flexion. All the records reproduced here were made with a vertically moving lever, the writing point of which was arranged vertically above that of the signal lever, and with the exception of fig. 4 they are one-third the amplitude of the actual excursion of the limb. Upward movement indicates extension and downward movement flexion (cf., Appendix). All the records are reduced to two-thirds their original size.

FIG. 2.—Modification in form of associated reaction on reversal of form of voluntary movement. The voluntary activities are as in the case of fig. 1, but extension precedes flexion. Voluntary extension (V.E.) produced a clonus-like oscillation and increased spasticity of the arm without any excursion of the forearm, while voluntary flexion (V.F.) evoked associated flexion.

voluntary extension produced a rapid oscillation of the flexed forearm in the initial posture (fig. 2).

In the case of the lower limb, the tendency to a stereotyped reaction was found to be more marked than in that of the upper limb. In the majority of cases the associated reaction was that already described, namely, limb extension, but in several patients flexion at hip, knee and

ankle (dorsiflexion) was constant irrespective of the form of the voluntary movement. Even here, however, a reversal of form of the associated reaction was occasionally observed in response to reversal in the voluntary muscular effort eliciting it. When voluntary flexion or extension was in question, the associated reaction was in some cases symmetrical, and in others opposite in form. In the case of abduction and adduction, however, as Raimiste [7] long since pointed out, the associated reaction is generally symmetrical, voluntary adduction being accompanied by associated adduction and conversely. Even this reaction was poorly developed at times, and it has to be remembered that in most cases of residual hemiplegia there is considerable voluntary power in the affected leg, and that it is impossible in these circumstances, and even in the normal subject, to adduct or abduct the extended limb without also bringing into action with equal force the corresponding muscles of the crossed leg.

The lower limb when under observation for associated reactions has to be supported by the observer in such a manner as neither to impede nor to facilitate unduly any reaction which may develop. When graphic recording is in question the limb has to be slung from the ceiling. It is obvious that by reason of its mass and length the lower limb is not well adapted to careful investigation, and possibly a more perfect technique might reveal that the tendency to constancy of reaction is less complete than at present seems to be the case.

In one patient reversal in the form of a tonic voluntary effort in the paralysed leg inverted the form of associated reaction in the paralysed arm, voluntary flexion against resistance leading to associated flexion and vice versa (fig. 3).

In this connection it is interesting to note the form of associated reaction in the paralysed arm which accompanies yawning and stretching. It is exceptional to find a subject with residual spastic hemiplegia from whom a history of spontaneous movement of the paralysed arm or hand on yawning cannot be obtained. In many cases, coughing is also accompanied by such a reaction. Every patient whom the writer has questioned on this point, with a single exception, has stated that the movement of the hand and digits in these circumstances is one of extension. This is often complete and is accompanied by fanning of the fingers. The forearm may be extended, but more commonly flexes and is raised up in front of the patient. Whenever the writer has observed this reaction to yawning, extension and separation of the digits have occurred. Moreover, two patients volunteered the state-

ment that when the fingers are extended and abducted during a yawn, they are able to flex and extend them rapidly, a thing they were unable to do at any other time. Indeed, one man added that he always waited for a yawn so that he might exercise his fingers in this way. In an earlier reference to this detail [17], the general inference was suggested that unilateral muscular contraction evoked an associated flexion, while such bilateral muscular acts as yawning evoked associated extension. In the light of the more recent observations recorded here, this general-

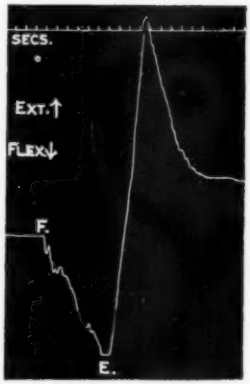


FIG. 3.

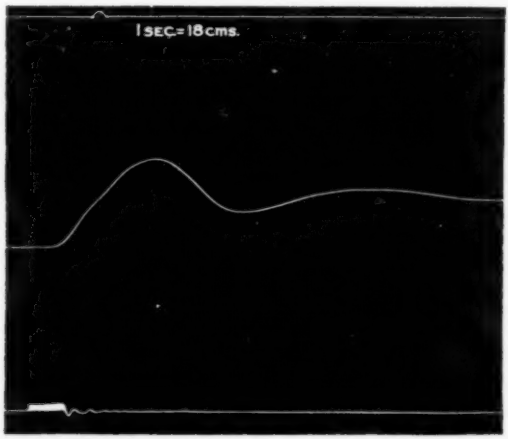


FIG. 4.

FIG. 3.—Inversion of associated reaction in hemiplegic arm on reversal of form of voluntary movement of homolateral leg. At F, voluntary leg flexion evoked associated flexion in the arm. At E, the leg is powerfully extended against resistance and associated extension in the arm occurs.

FIG. 4.—Graphic record of supinator jerk from hemiplegic arm of patient from whom figs. 1, 3, 6 and 7 were also taken. With the method of determining latency which was adopted (cf. Appendix) the latent period is seen to be 0·04 second (40 σ). With the same method, the latency of associated reactions and other tonic reflexes described is seen to be much longer. With a more perfect technique, Jolly found the average latency for the knee-jerk in man to be 0·02 second.

ization must be abandoned, yet it remains a striking fact that the form of muscular activity most commonly producing associated extension of the digits is bilateral. In this case, the stimulus may be tonic contraction of the diaphragm.

(4) *The latency and duration of the associated reaction.*—When we come to consider the latency and duration of associated reactions we gain an insight into their probable nature. In a large series of obser-

vations, the following values were obtained for the latencies in different cases: 0·25, 0·5, 0·75, 1·0, 1·5, 1·75, 2·0 seconds. If we compare this with the latency of such a phasic reflex as a tendon jerk, the contrast is striking. Fig. 1 is the graphic record of two associated reactions (flexion and extension at the elbow) in the hemiplegic arm of a patient whose supinator jerk is recorded in fig. 4. The method of obtaining the latency was the same in the two instances. The latent period of the associated movement is 0·75 second, while that of the supinator jerk is 0·04 second. It will be noticed that both records show the characteristic " shortening reaction " of tonic muscle.

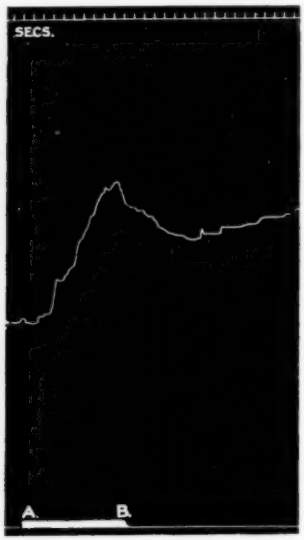


FIG. 5.—Associated reaction in hemiplegic arm from a patient with infantile hemiplegia. The tonic after-contraction persisted for over 40 seconds. The first 18 seconds are seen in the record. The stimulus—a forceful grasp of the normal hand—is seen to have lasted 10 seconds (A—B).

The duration of an associated reaction is roughly that of the voluntary movement or contraction evoking it, but there is in some instances a prolonged after-contraction or tonic prolongation of the spasm which may last for several seconds. In one case this was still of undiminished intensity after the lapse of 40 seconds (fig. 5).

While the reaction persists, the limb maintains the new attitude

more or less steadily, but occasionally there may be a fine tremulous oscillation round a fixed point. In one instance the rate of this oscillation was 6 per second, and the tremor resembled the ordinary clonus of a spastic limb.

In general, it may be stated that the more spastic the limb, the longer the latency and after-contraction, though the amplitude of the limb excursion may be small. In one case in which spasticity was slight, the latency was always less than a second, commonly 0·25 second, the limb excursion was ample and rapid in rise and there was practically no after-contraction, the limb having returned to its initial position within 0·5 second of cessation of the stimulus (grasp of normal hand).

(5) *Inferences as to the nature of the associated reactions.*—We have seen that associated reactions are evoked most typically by voluntary tonic contraction of muscles. They are not produced by rapidly alternating voluntary movements unless these are widespread or forceful, and they cannot be produced by cutaneous stimuli apart from such tonic contraction. In short, the adequate stimulus is proprioceptive and of some duration. The response has a comparatively long latent period, is commonly slow in development and lasts, and may outlast, the duration of the stimulus. The reacting muscles go into strong tonic contraction, which produces, with rare exceptions, an excursion of the limb of variable amplitude. The limb takes up a new posture which persists until the stimulus producing it ceases. Therefore, in respect of stimulus, latency, form and duration the associated reaction presents all the characters of a tonic or postural reflex. Usually, the seat of the stimulus is the musculature of one of the normal limbs, but strong voluntary contraction of a partly paralysed leg may give rise to a well-marked associated reaction in the homonymous arm.

Chapter III.—Other Tonic or Postural Reactions in Hemiplegia.

We have learned from the researches of Sherrington and Magnus that decerebrate rigidity and normal tone may be influenced by afferent impulses arising in the labyrinths and in proprioceptive end-organs in the musculature and other deep structures of the neck and body wall. The function of these reflex variations in muscle tone is to produce the various attitudes of the animal. If, therefore, the spasticity of hemiplegia is physiologically identical with decerebrate rigidity, we should

expect to find evidence of these reactions in the affected muscles in cases of hemiplegia. Indeed, several observers have recorded such reactions in man (Magnus and de Kleijn [3] [4], Brouwer, Marie and Foix [6]). While we may safely conclude that the occurrence of tonic neck reflexes in man has been established in various clinical conditions, labyrinthine reflexes have been much less frequently observed, and in the majority of cases in which neck reflexes have been recorded there have been no clear indications of labyrinthine influence on tone.

(1) *Tonic neck reflexes.*—In the spastic cases examined for these reactions, the general rule was that at the beginning of the investigation, and with the patient standing, rotation of the head on the neck produced no excursion of the hemiplegic arm, and it was not until the examination of the associated reactions had been carried out, the patient placed in a supine position, or vigorous passive movements of the paralysed arm performed, that active neck reflexes developed. Occasionally, however, these reactions were very facile and active from the outset. As the patient stood erect with the affected arm semi-flexed and adducted, voluntary rotation of the head to the paralysed side, especially if carried out with force, evoked a slow but powerful tonic extension of the arm, which was maintained until the head was turned back again to the median position, or across to the normal side. Associated with the extension, the arm was generally slightly advanced and adducted, and the forearm went into full pronation. The wrist extended and the fingers clenched tightly. Rotation of the head from the paralysed side, or from the median position, so that the patient looked over the normal shoulder, was followed by a movement of flexion of the forearm and slight return to supination. The upper arm was commonly adducted, but in some patients there was abduction and elevation. The form of this tonic reaction, both to direct observation and in a graphic record, was very characteristic. The latent period was distinctly long, and the following values were obtained in different patients under the same conditions of recording: 1·0, 1·25, 1·6, 2·0, 3·5, 5·0, 6·0 seconds. From the moment of onset of the response to that of maximal excursion of the reacting limb, a period of from 0·5 to 2 seconds elapsed, but in this respect there was considerable individual variation. In one patient, after a latent period of about 1 second the limb shot rapidly into its new posture, remained there for from 5 to 6 seconds and then returned to its initial attitude. In general, however, the new posture was maintained until the patient turned the head back to the original position (fig. 6).

Care was taken to ensure that in rotating the head the subject did so steadily and without jerking, and the average period during which the movement of rotation was carried out was from six to ten seconds. It was when the movement was well under way that the slow movement of the reacting arm to its new posture began.

In two patients passive rotation of the head by the observer evoked forceful variations in the attitude of the paralysed arm and leg, but, in general, voluntary movement was essential.

At some period of a systematic examination of the postural reactions, or in some at least of a series of such examinations, these tonic neck

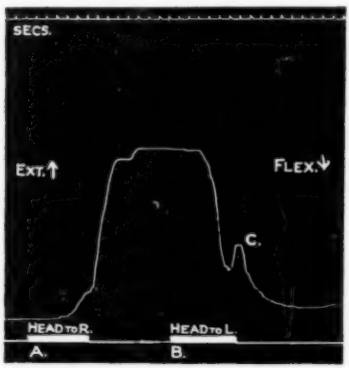


FIG. 6.—Tonic neck reflex in hemiplegic arm. At A on signal line, the head was voluntarily rotated to the paralysed side through an angle of approximately 180 degrees from its initial position with the face looking over the normal shoulder. After a latent period of about two seconds, and while rotation was still in progress, a tonic extension developed in the arm. At B, the head is rotated back to its initial position, and again after a similar latent period the tonic extension gives place to tonic flexion, the arm regaining its original posture of semi-flexion at the elbow. During this return a short spasm of extension is seen to occur at C. The head rotation occupied six seconds and was carried out without undue force.

reflexes were present in greater or less degree in every patient examined. When they were not evident at first, the practice was to make the patient lie on his back on a couch for a few minutes, after the lapse of which the reactions began to appear on appropriate stimulation, that is, on rotation of the head. There could be no doubt that their appearance was facilitated by a preliminary examination of the associated movements, and it was found that after half an hour's examination and manipulation of the paralysed arm the reactions were at their maximum for the individual patient. When fully developed,

rotation of the face towards the paralysed side evoked extension, and rotation to the sound side flexion. This result is in strict accord with Magnus's observations.

Inclination of the head to one side ("Wendung" in Magnus's nomenclature) was not found to evoke any reaction in the cases so far examined, but it is possible that further investigation may reveal a neck reflex evoked in this way. In the case of the lower limb, the influence of variations in head posture in relation to the trunk was distinctly less constant, and when present less marked than was the case with the upper limb. The commonest finding is that rotation of the head produces an increase in extensor rigidity in the paralysed leg, whether rotation be towards or away from the paralysed side. In one patient, however, with a profound degree of right hemiplegia from cerebral tumour, active and passive rotation of the head towards the paralysed side evoked powerful extensor spasm in both arm and leg, and rotation to the normal side evoked active flexion spasm in the arm, and a pronounced diminution of extensor spasm in the leg.

Finally, when head rotation seems to be entirely without effect, the presence of a latent influence on limb tonus can be demonstrated for the paralysed limbs by eliciting associated movements with the head in different positions. Observations in this sense have been reported by Simons [12] [13], and the writer's own results are in strict accord with those recorded by him. This effect will be described in the following chapter.

(2) *Tonic labyrinthine reflexes.*—In the decerebrate animal, the reinforcing influence of the labyrinths on extensor tonus in the limbs was found by Magnus and de Kleijn [3] to be minimal when the animal is in the standing position and the head so held that the line of the mouth ("Mundspalte") makes an angle of about 45 degrees below the horizontal, and maximal with the animal in the supine position and the line of the mouth making an angle of about 45 degrees above the horizontal. In an infant with amaurotic family idiocy examined by these observers, both neck and labyrinthine reflexes were found to be very active, and they were able to determine that the maximal and minimal positions were practically identical for the human subject with those found for quadrupeds (cat, dog, monkey). In hemiplegia, therefore, we should expect to find labyrinthine influence maximal with the patient in the supine position and the head slightly retracted, and minimal with the patient standing, sitting or prone, when the face points downwards to the ground and a perpendicular drawn out from the face making an

angle of about 45 degrees below the horizontal. This, in fact, is what has been found to be the case, as observations recorded in a later chapter indicate.

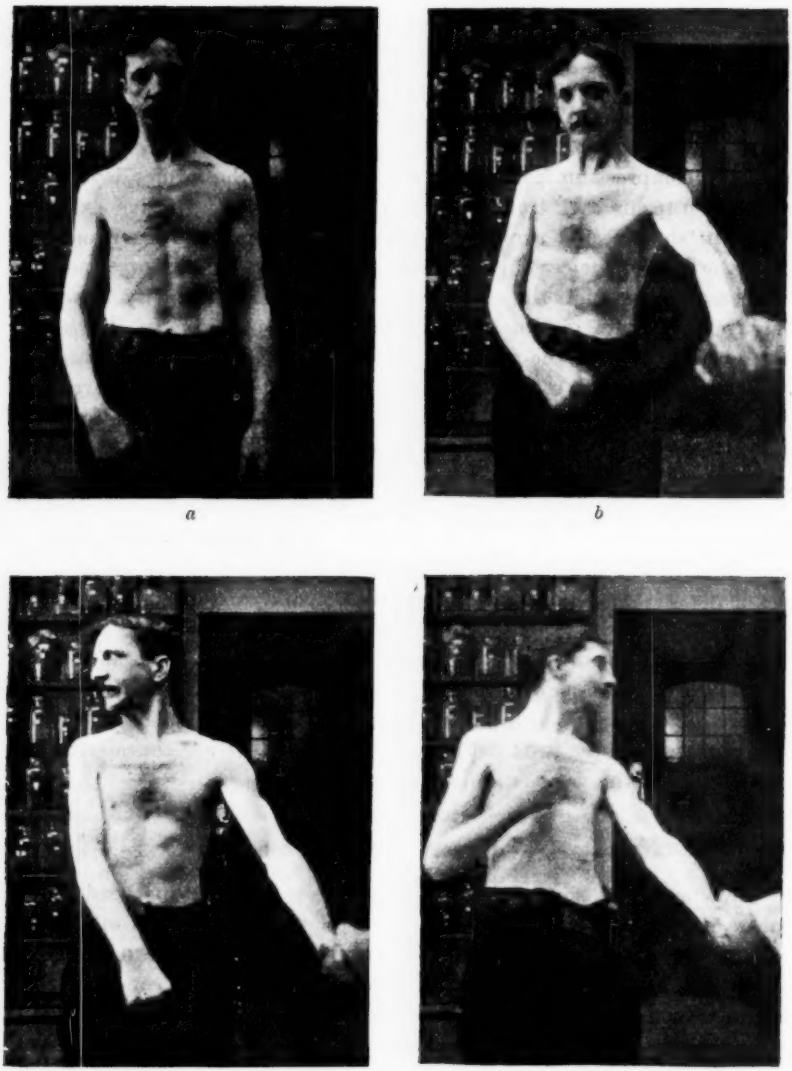
In the cases under examination, fully developed labyrinthine reflexes were not observed. The clearest indications were obtained from two patients with right hemiplegia (one thrombotic in origin, and one the result of compression from cerebral tumour). In the former, laying the subject on to his back from a sitting position evoked no active extensor tonus in the affected arm, but when he lay prone and the arm hung over the side of the couch, it was clear that it had taken up a posture of increased flexion at the elbow, despite the action of gravity, now that labyrinthine influence on extensor tone was minimal. In the latter, laying her back into the supine position from a sitting position evoked a marked and forceful extension spasm in the previously flexed arm. It was not possible to examine her in the prone position, as the ordinary hospital bed is not suitable for the purpose and she could not well be moved on to the hard narrow couch used for this purpose.

We have seen, however, that even in those patients where tonic neck reflexes cannot be demonstrated directly by simple head rotation, the existence of strong tonic influences arising in the neck proprioceptors can be demonstrated by studying the profound modifying effect on associated reactions of head rotation. This is equally true of labyrinthine influence, and the investigation of associated reactions with the patient in the lateral, prone and supine positions indicates that the labyrinths do influence tone in the hemiplegic arm, if not very obviously in the leg. The results of these tests will be described when we are considering the interaction of the various tonic reflexes.

Chapter IV.—Interaction of Tonic Reflexes.

We have said that in those cases where rotation of the head on the neck and variations in head posture in relation to the horizontal plane do not evoke tonic reactions in the hemiplegic limbs, that nevertheless both neck and labyrinthine influences are at work and can be demonstrated by studying the effect of changes in head posture in relation to trunk and to space on associated reactions obtained in the manner described. We shall now proceed to study some examples of this interaction of tonic reflexes.

(1) *The influence of neck reflexes on associated reactions.*—When the neck reflexes are active, the familiar associated flexion of the hemiplegic



a *b*

c *d*

FIG. 7, *a*, *b*, *c*, *d*.—Inversion of associated reaction in hemiplegic (right) arm by neck reflexes: *a* = resting position of hemiplegic right arm; *b* = flexion-adduction reaction to a forceful grasp with the right hand with the head in the median position; *c* = extension-adduction reaction with full pronation of the forearm, when the head is rotated towards the hemiplegic side; *d* = flexion reaction when the head is rotated to the normal side.

arm on forceful tonic contraction (grasp) of the normal arm may be completely inverted in form when the head is rotated to the hemiplegic side, that is, with face pointing over the shoulder of the affected half of the body. The photographs below (fig. 7 (*a*), (*b*), (*c*), (*d*)) show this more clearly than any verbal description. This patient has a cerebral thrombosis of five years' standing. An identical state of affairs is

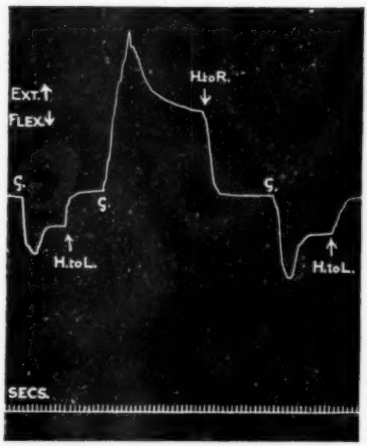


FIG. 8.

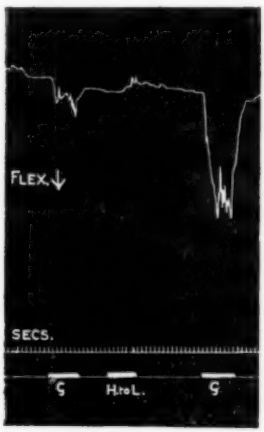


FIG. 9.

FIG. 8.—A graphic record of the same phenomena from a patient with left hemiplegia. The initial posture of the head is full rotation to the right (normal side). At G a voluntary grasp with the normal hand evokes associated flexion of the hemiplegic arm with incomplete return ("shortening reaction") on relaxation of grasp. The head is then rotated to the hemiplegic side (H to L). At once further extension to the original posture of the arm occurs. At G, a grasp with the normal hand is now accompanied by strong associated extension in the hemiplegic arm with incomplete return on cessation of grasp. The head is again rotated to the normal side (H to R), and the arm returns to its original posture. At G, voluntary grasp with the normal hand is followed by associated extension and incomplete return as at the beginning of the record. Therefore, the record shows inversion of associated reaction by neck reflex, and also the characteristic "shortening reaction" of tonic muscle.

FIG. 9.—Shows a less profound influence of neck reflex on form of associated reaction than is seen in fig 8. A case of right hemiplegia. With the head rotated to the hemiplegic (right) side, voluntary grasp evokes a clonus-like oscillation of the hemiplegic arm in its initial posture. On rotation of head to normal (left side), the associated reaction is flexion.

revealed in fig. 8. This graphic record is taken from a case of embolic left hemiplegia of two years' standing. It shows in addition to reversal in form of associated reaction, the "shortening reaction" so characteristic of reflexes in tonic muscle. After cessation of the voluntary grasp of the normal hand, the associated flexion or extension passes off incompletely, but with rotation of the head the limb returns at once to

its initial posture. However, the influence of the neck reflexes is not always so potent, and in some subjects the associated reaction is modified but not inverted. Thus, fig. 9, taken from a patient with right hemiplegia of thrombotic origin, shows an associated reaction consisting simply of increase of tone and oscillation of the limb round the initial posture when the head is rotated to the paralysed side, but associated flexion when the head is rotated to the normal side. With the head in the median position a slighter degree of flexion occurred. Fig. 10

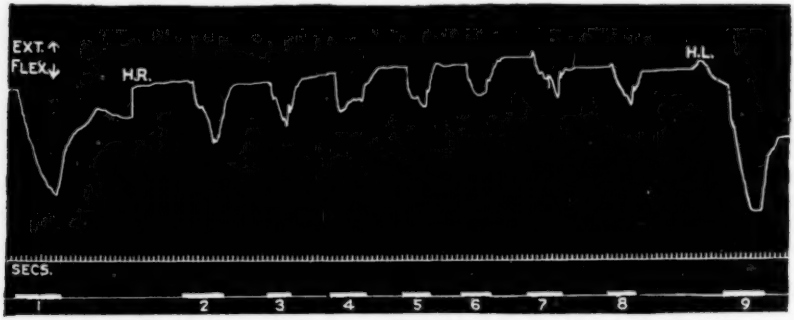


FIG. 10.—Shows a still less marked influence of neck reflex on the associated reaction of the hemiplegic arm. The reaction is not inverted in form, but the associated flexion is diminished progressively in amplitude and force with each successive grasp after the head has been rotated from the normal to the hemiplegic side. Rotation of the head to the normal side after a series of voluntary grasps produces on a further voluntary grasp a full flexion reaction in the hemiplegic arm. The first and last (1 and 9) associated flexion reactions were obtained in the manner described with the head rotated to the normal side. The head was then rotated towards the paralysed side, and a series of grasps performed with the normal hand (2 to 8). A progressive diminution of the associated flexion is seen with each grasp, and the base line rises, indicating a gradual opening out of the angle between forearm and upper arm. On rotating the head back again towards the normal side, a greatly increased flexion reaction at once ensues on grasping. This reaction is more ample than the original one, and may be said to show the phenomenon of "post-inhibitory exaltation." Further, a "shortening reaction" is to be seen after the first and last reaction.

records an even less marked influence of the neck reflex. The patient had a thrombotic right hemiplegia of two years' standing. In both positions of the head (rotation to right and to left) the associated reaction in the affected arm was flexion, but with the head rotated to the normal side the flexion was more ample and more forceful than with the head rotated to the paralysed side. In the latter instance, each successive associated reaction is less ample and the return to the initial posture less complete, so that the angle between forearm and upper arm gradually opens out. Finally (grasp 9), the head is again rotated to the

normal side and a more ample associated flexion than was present originally is seen to occur. This increased amplitude may be regarded as an example of "post-inhibitory exaltation."

(2) *The influence of labyrinthine reflexes on associated reactions.*—This is best seen by examining the associated reaction in the hemiplegic arm with the patient in the positions of maximal labyrinthine influence (supine) and of minimal labyrinthine influence (prone). In the patient whose reactions are illustrated in fig. 7, the associated reaction with the patient standing and the head in the median position is slight flexion at the elbow. In the supine position, on two separate occasions, the reaction was extension, pronation and slight advancement of the upper arm. On these two occasions, on turning the patient over on to his face (prone), with the head slightly retracted and the arms hanging free at the sides of the narrow couch, the hemiplegic arm at once took up a posture of increased flexion, despite the unantagonized action of gravity on the limb. In these circumstances, the associated reaction was ample flexion with some abduction at the shoulder. Similar results were obtained with the patient sitting upright in a chair. When the head was well thrown back (maximal position of labyrinthine influence) and in the median position, the associated reaction was extension of the affected arm, but with the patient sitting well forward and the head bent downwards and the face gazing between his knees (minimal labyrinthine influence) the reaction was flexion.

Apart from this direct modifying effect of labyrinthine impulses on the form of the associated reaction, a general reinforcing effect upon both neck reflexes and associated reactions often follows placing the patient in the prone position, and this also we may attribute to the labyrinthine influence on tone.

(3) *The interaction of associated reaction, neck and labyrinthine reflexes.*—It is clear from what has been said that at any given moment an associated reaction is the resultant of at least three factors: the form of the stimulus (voluntary tonic contraction), the position of the head in relation to the horizontal plane (labyrinthine influence) and the position of the head in relation to the trunk (neck influence). It follows, therefore, that in an examination of associated reactions in which none of these factors is constant we may obtain a bewildering diversity of reactions in the hemiplegic arm, which seem to be governed by no very evident laws. In the study of associated reactions undertaken in 1912-1914 only one of these factors, and that not the most important, was taken into account. It was observed that sometimes

a reversal in the form of the voluntary effort eliciting the associated reaction did effect a reversal in the form of the latter, but this was not constant, and sometimes the reaction was symmetrical and sometimes in the opposite sense. We can see now, however, that no constancy of result was to be expected unless and until the influence of head posture was taken into account. In one of the patients of the first series a stereotyped associated flexion of the hemiplegic arm was obtained no matter what the form or the situation of the voluntary effort evoking it. The observation now gains interest, for the record contains a note that the patient always turned his head to the right (normal side) when carrying out any forceful voluntary movement. It is not too far-fetched, perhaps, to conclude that this rotation of the head away from the paralysed side was a determining factor in the constant form of the associated reaction.

Since labyrinthine and neck influence are always in question, it follows that in the different positions of the subject they must combine variously, sometimes reinforcing and sometimes antagonizing each other. This can be tested by examining associated reactions with the patient in the supine, prone and lateral positions with the head in the median, right and left relations to the trunk. This somewhat complex examination is best illustrated by an actual example. A. C., a case of thrombotic right hemiplegia (cf. figs. 1, 3, 6, 7).

First position—standing. Arm hangs as in 7, *a*. Voluntary movement throughout examination consists in a forceful voluntary grasp with the left hand, the left arm being extended and adducted and slightly advanced.

Head centre = slight flexion at elbow.

Head right = extension, pronation and advancement.

Head left = flexion at elbow.

Second position—supine. Arm slung in same degree of flexion as fig. 7, *a*. Voluntary movement as in 1. Head slightly retracted.

Head centre = some extension, pronation and adduction.

Head right = full extension and pronation.

Head left = flexion to right angle.

Third position—prone. Arm hanging free at side of couch and flexed to an angle of about 120 degrees with upper arm. Head slightly retracted. Voluntary movement as above.

Head centre = flexion to right angle with slight abduction.

Head right = moderate extension with marked adduction.

Head left = full extension with pronation and slight adduction.

Fourth position—right lateral. Elbow lies on couch anterior to trunk in moderate flexion. Voluntary movement as above.

Head centre = flexion.

Head right (i.e., face looking downwards on to pillow, occiput above) extension.

Head left (face up, occiput down) = extension.

Fifth position—left lateral. Hemiplegic arm now uppermost and slung in moderate flexion. Voluntary movement as above.

Head centre = flexion.

Head right (i.e., face up, occiput down) = extension.

Head left (i.e., face down, occiput up) = flexion.

These results become intelligible if we bear in mind that labyrinthine influence on extensor tone is maximal with the head slightly retracted and the face looking upwards, and minimal with the head slightly retracted and the face looking downwards. Therefore, with the patient supine we should expect to find an extensor reaction (if labyrinthine reflexes are active) with head centre as well as with head right (i.e., turned to paralysed side). In the prone position, on the other hand, labyrinthine influence being minimal, we should expect to find neck reflexes predominating and a flexor associated reaction with head centre and head left. This is what we have actually found to be the case. In the lateral positions with the head median, labyrinthine influence is intermediate in potency (less than in supine and more than in prone positions), and here the neck reflexes determine the form of the associated reaction. With the face pointing upwards, however, labyrinthine influence increases and we see associated extension in both lateral positions, though in the right lateral position this involves rotation away from the paralysed side. With the face pointing downwards labyrinthine influence is minimal, and here again the neck reflexes determine the form of the associated reaction. Therefore, in the right lateral position we get associated extension when the face points downwards (that is, head rotation to right) (paralysed) side, and in the left lateral position with the face pointing downwards (head to left) (normal) side we get associated flexion.

We see, therefore, that a rapid method for determining the relative predominance of labyrinthine and neck reflexes in a case of hemiplegia, is to place the patient in that lateral position in which the hemiplegic side is downmost and the normal side uppermost. If, in these circumstances, rotation of the head so that the face points upwards produces associated extension in the hemiplegic arm (that is, when face is turned away from hemiplegic side) then the labyrinthine influence is present and active. If, however, flexion results then the neck reflex predominates.

One further complicating factor remains for mention. If each of a series of patients is subjected to repeated examination on different days, it may be found that on one occasion the neck reflexes predominate in all positions of the head in space, while on another the labyrinthine influence is the more potent. As was observed before [15] when dealing with the reflex phenomena in spastic paralysis of the lower limbs, reflex reactions in tonic extensor muscles vary far more widely from day to day than the phasic reflex reactions obtained from flexor muscles.

Thus in a spastic paraplegia in extension, the form, receptive field and activity of the flexion reflex varies little if at all from day to day, but the degree of spasticity, the presence of clonus and of other reactions in the extensors is much more variable. This is equally true of the tonic reflex reactions now under consideration. The conclusion to be drawn from this is that repeated examination on different occasions is essential if we are to obtain a clear notion of what tonic reflexes are present in a given subject with hemiplegia. Such variations as may be detected from day to day, however, do not indicate that associated reactions are capricious phenomena governed by no discoverable laws. They indicate that there are several factors at work in determining the form of an associated reaction, or the presence and activity of a tonic neck or labyrinthine reflex; that the relative potency of these different factors varies slightly from day to day and from hour to hour, according to the external circumstances (such as external temperature, fatigue, &c.) obtaining; and that patient and repeated examination will reveal that four determining factors are always operative, though in varying degrees of intensity. These factors are: (1) the form of the voluntary effort eliciting an associated reaction. This is relatively unimportant in our experience. (2) The presence of tonic impulses arising in the proprioceptors of the neck; (3) the presence of tonic impulses arising in the otolith organs of the labyrinths; and (4) the manner in which neck and labyrinthine influences combine.

Chapter V.—Relation of Associated Reactions to other Tonic Reflexes.

In our endeavour to determine the nature and physiological significance of associated reactions, we may compare them with the tonic neck reflexes, for it is undisputed that these are reflex postural reactions. From the observations recorded here there can be little doubt that the familiar associated reactions of the paralysed limbs in

hemiplegia are phenomena of the same order as the tonic neck reflexes of Magnus and de Kleijn. An observer looking at an associated reaction in the paralysed arm produced by a tonic grasp with the normal arm, and comparing it with the tonic neck reflex occurring in the paralysed arm on rotation of the head, cannot distinguish the two; they are identical in form, latency and duration. If there be any distinction between the two, as they occur in a given subject, it is that the tonic neck reflex tends to have a slightly longer latency, to develop more slowly, to have a longer after-contraction and to subside less suddenly. These points of difference, which are never more than a matter of one or two seconds, can readily be traced to the character of the stimulus in each case. In the associated reaction, the stimulating grasp is more forcible, develops more rapidly and ceases more suddenly than is the case with the leisurely rotation of the head which produces the tonic neck reaction. In both instances, the limb goes into strong tonic contraction, predominantly flexor or predominantly extensor as the case may be, and takes up a new posture which is maintained until the proprioceptive stimulus ceases. We may conclude, therefore, that the associated reactions which follow strong tonic voluntary muscular contraction in hemiplegia are postural reflexes closely allied with the tonic neck and labyrinthine reflexes of Magnus and de Kleijn.

In the introductory chapter we mentioned the pioneer observations of Sherrington that the tone of a given muscle, although dependent for its maintenance on the afferent nerve supply of that muscle, yet was capable of modification, or regulation, by means of afferent impulses arising elsewhere. As we have seen, the later work of Magnus and his collaborators has resulted in the minute analysis of the nervous reflex mechanisms by which this regulation of tone is carried out. However, these observers make no reference to tonic reflexes arising in the limbs themselves and regulating the posture either of the head, trunk or limbs. Yet a moment's consideration will suggest that the existence of such reactions is extremely probable, for voluntary activity of the limbs may be such as to demand widespread synergic postural fixation, and it is the experience of everyone that such fixation occurs in all forcible muscular activities of the limbs. Moreover, we do not turn in vain to experimental physiology for confirmation of these conjectures. Sherrington [9] has recorded that "The reflex posture in each body-region is not of course wholly independent of afferents in other regions. Thus, passive flexion of the elbow and shoulder often provokes in the decerebrate preparation heightening of the tonic extension of ipsilateral

knee and ankle, and lowering of it in crossed knee and ankle. Again, active or passive rotation of neck on its long axis in the decerebrate preparation inhibits extensor tonus in hind-limb on the side of the lowered pinna and causes active flexion of the knee . . . ." Here we find grouped together, as reactions of the same order, tonic reflexes arising in the limbs and acting on the limbs, and tonic reflexes arising in the neck and acting on the limbs. This is exactly what we have described as occurring in hemiplegia. The associated reaction in the paralysed arm on voluntary clenching of the normal hand is a tonic reflex arising in the limb and acting on the (crossed) limb. When they are the result of contraction of trunk muscles, as in yawning, they may be called " tonic reflexes arising in the trunk and acting on the limbs." In the same way, the associated tonic reactions of the trunk muscles may be classified according to whether they depend upon voluntary contraction of trunk or of limb muscles.

If we accept this view as to the nature of " associated movements " in hemiplegia, we are not postulating as essential to the co-ordination of posture in man any factor or process which has not already been demonstrated to obtain in mammals, from the guinea-pig to the ape.

It is not necessary to recapitulate the reasons given in a previous chapter for regarding " associated movements " as tonic reflexes, but we may now emphasize, as further confirmation of that conclusion, the manner in which they act harmoniously with the tonic neck and labyrinthine reflexes, each group reinforcing and modifying the other two. Nevertheless, certain alternative interpretations have to be considered. Marie and Foix [6] speak of the reactions in question as " syncinésies globales," and regard them as one of three distinct types of associated movement to be observed in cases of hemiplegia. We are not now concerned with the second and third types, though it will be necessary to refer to them later. Marie and Foix state that " syncinésies globales " consist, as the term indicates, of a generalized contraction of the muscles of the reacting limb in which there is a struggle between flexor and extensor groups, one or other predominating and determining the direction of the movement. In effect, the result is simply an exaggeration of the type of spasticity already present in the limb, flexion in the arm and extension in the limb. They state further that for a given patient the form of the global associated movement is constant under all conditions and incapable of variation. Now, if we accept this view we seem compelled to deny that associated movements are reflex reactions, for in no known reflex is this complete overthrow of co-ordinated activity to

be observed. All postural and phasic reflexes show either simple reciprocal innervation or the more complex double reciprocal innervation. In view of the observations here recorded, it seems impossible to deny the reflex origin of associated movements, and therefore we need not give further consideration to Marie and Foix's implication. However, it is the fact that antagonistic muscle groups, extensor and flexor, are to be observed in simultaneous contraction in such an associated reaction as we have described. Riddoch and Buzzard [8] have emphasized this point, and evidently felt the difficulty of reconciling it with their conceptions of reflex co-ordination of movement. Hence they came to the conclusion that while reciprocal innervation obtains in phasic reflexes, that is in reflex movements, postural reflexes are governed by a distinct process of concurrent innervation. It is not necessary to modify or add to the laws governing the reflex co-ordination of movement which have already been formulated. Sherrington [10] has pointed out that simple reciprocal innervation is "a relatively artificial reaction" because: "The isolated stimulation of just one whole afferent nerve, the rest of the nervous system lying plunged at the time in approximately complete quietude, is a state of things little resembling the ordinary occurrences of waking life. Usually in the latter the reactions of the nervous system result from the combination of a number of stimuli playing concurrently on its afferent channels, and some impelling to one action and some to another. Any particular motor centre, whether for flexion or extension, lies then under at least a twofold influence. . . . If we voluntarily hold the arm semi-flexed, nothing is easier than to make both flexor and extensor contract together; by simply feeling the hardness of the muscles through the skin we can assure ourselves of that fact. . . . Certain reflex reactions in their natural occurrence similarly exhibit in some cases a contemporaneous contraction of antagonists." If, in an experimental preparation, two stimuli, one exciting flexion and one extension of a limb, are simultaneously given, it is possible by suitable grading of the two to produce a flexion movement in which both flexors and extensors are simultaneously in contraction. What is observed is that flexion is less pronounced than it would have been with a single flexion stimulus, while inhibition of the extensors is also less complete. The discharge from both flexor and extensor half-centres represents the algebraical sum of the opposed excitation and inhibition. We see, therefore, that it is not right to assume "that under reciprocal innervation two antagonists necessarily can never be in contraction at the

same time. . . . What reciprocal innervation does provide is that, in the execution of a muscular act by antagonists, augmentation of contraction or motor discharge shall not occur concurrently in protagonists and antagonists, nor conversely decrease of contraction or discharge occur concurrently in the two. These latter appear only possible when, breaking in on a condition of rest of both half centres or opponent muscles, there ensues one of those instances of double reciprocal innervation in which the balance between inhibition and excitation is such as to allow both half-centres to discharge, although unequally ; or when to such a state of double reciprocal innervation there succeeds a reversion of both half-centres into rest, the stimuli which evoked the double reciprocal innervation subsiding together. Except under these circumstances, reciprocal innervation secures that any increase in the contraction or discharge of the protagonists shall be accompanied by corresponding diminution of the contraction or discharge of its antagonist, even to complete suppression of the latter." It is scarcely possible to explain this complex process of reflex co-ordination of movement and of posture more succinctly, hence these long quotations from Sherrington may be pardoned. The relation of opposing groups of muscles in so complex a reaction may be summed up in the striking phrase of Hughlings Jackson, employed originally it is true in another connection, but equally apt in this, that there is between the two " a perfect co-operation of antagonism." We are not, therefore, compelled to reject as a true reflex reaction one in which there is visible simultaneous contraction in opposing muscle groups. Moreover, it is clear that in a maintained attitude this simultaneous activity will be more readily visible than in a rapid movement of the limb. In short, the final difficulty in regarding " associated movements " as true reflex reactions has been removed.

There remains one other possible interpretation. Socin and Storm van Leeuwen [14] have shown that the presence of a tonic neck reflex may modify the form of a phasic reflex simultaneously elicited, and the interaction of tonic neck and limb reflexes we have described may be an example of such a variation in a phasic reflex (the associated reaction) by a concurrent tonic reflex (the neck reflex). We have only to consider this possibility to dismiss it. As Riddoch and Buzzard have shown, phasic reflexes in the upper limb differ in the quality of the stimulus and in the nature of the response from the associated reactions we have been considering. In every factor concerned, the latter present unmistakably the characters of tonic or postural reactions.

We mentioned earlier a classification of "associated movements" advanced by Marie and Foix, and if we are to orientate the interpretation of these phenomena reached in the present paper, we must consider shortly the views of these observers, whose paper on the subject is at once the most recent and the most comprehensive on the subject. It will be seen that they employ the term "syncinésies" in a much wider sense than that commonly understood by the term "associated movements" in this country. The associated reactions described in Chapter II of the present paper are the "syncinésies globales ou spasmodiques" of Marie and Foix. The second group of these writers is that of "syncinésies d'imitation." These are stated to be rare and of little theoretical importance. They are largely voluntary, and can be inhibited by the subject. They consist in feeble imitative movements in one limb when its fellow carries out rapidly alternating movements. They are to be seen in cases where there is no question of a pyramidal lesion, and occur indifferently in the normal or in the affected hand in such conditions as hemichorea, and hemiathetosis. Marie and Foix consider that they represent an exaggeration of the normal tendency to imitation by the crossed hand or arm of alternating movements. It seems, therefore, that on this definition the movements in question are neither reflex nor tonic, and can be called "associated" only in a loose sense of the word. Under the heading "syncinésies de co-ordination" we find included a somewhat varied collection of motor activities, tonic, phasic, reflex and voluntary, and having for the most part nothing in common. Thus, Magnus and de Kleijn's tonic neck reflexes find a place here, and are stated to be fundamentally distinct from the associated reactions produced by voluntary contraction of muscles. Quite distinct from this group is the phenomenon the description of which follows. A patient with some voluntary control over the affected leg may be unable to dorsiflex the foot as an isolated movement, yet when he is asked to flex the whole limb dorsiflexion of the foot occurs and cannot be inhibited. In these circumstances they regard dorsiflexion as an associated movement. This conclusion seems to embody a conception of the nature of hemiplegia which has not been held in this country since Hughlings Jackson gave us a more profound insight into the matter [2]. We know that isolated movements, especially of the distal segments of the limbs, are the first to suffer in a condition of hemiplegic weakness, while the more deeply organized mass movements of the limbs, which have a complete representation on the reflex levels of the nervous system, are very much more resistant. In every case

of residual hemiplegia, we may find abundant illustration of this law of dissolution of function in the nervous system. Therefore, to speak of dorsiflexion of the foot when it occurs as an *integral part of another movement* as an "associated movement" is to stretch the conception of associated movements to a point when it ceases to have any precise meaning. We may conclude, therefore, that interesting as Marie and Foix's classification undoubtedly is, yet it cannot be accepted as based upon a truly scientific analysis.

Chapter VI.—Conclusions.

As the result of a study of the so-called "associated movements" of hemiplegia undertaken during 1912-1914, the general conclusion was reached that they are rather to be regarded as postural reactions, that is, as variations in muscle tone and attitude, than as movements in the strict physiological sense. No precise determination of the factors governing the form of these reactions, nor of their relation to other varieties of tonic reflex reaction, was reached. In the period which has elapsed since these observations were made, there have been striking advances in our knowledge of the nervous processes by which the regulation of tone, that is, the co-ordination of posture, is achieved. The experimental researches of Magnus and de Kleijn and their collaborators must be specially mentioned in this connection, and in the light of this knowledge a re-survey of the problem has been attempted.

It is found that the nature of the adequate stimulus, and the latency, form and duration of these reactions, confirm the view that they are in fact tonic or postural reflex reactions and not "movements" in the strict physiological sense of this term. The adequate stimulus is a tonically maintained voluntary contraction of some part of the skeletal musculature other than the reacting muscles. Forceful tonic contraction of the normal arm is the most powerful stimulus, and no actual excursion or movement is necessary. The response has a characteristically long latent period, in which it differs strikingly from such a phasic reflex as a tendon jerk, is tonically maintained throughout the period of stimulation, develops relatively slowly and as slowly declines, and may show marked tonic after-contraction and "shortening reaction."

When the conditions of investigation are unchanged, the response tends to be invariable in form. The common type consists of increased

flexion of the forearm and of the wrist and digits, with variable movement of the shoulder, in which either adduction, abduction or elevation may predominate. In the leg the common response is increased extensor rigidity with some inversion and dorsiflexion of the foot and dorsiflexion of the hallux. Other less common forms are described.

It is found also that not infrequently the "associated reaction," for such it seems more accurate to call it, may be profoundly modified in form by variations in the form of the voluntary contraction eliciting it. Thus, the response to voluntary flexion of the normal arm may be an associated flexion attitude, while on voluntary extension associated extensor spasm may result. On the other hand, reciprocal responses may occur. Such modifications of response are more commonly observed in the upper limb, but are occasionally to be seen in the paralysed leg.

A search for the *tonic neck and labyrinthine reflexes* described by Magnus and de Kleijn was also made, and it was found that, in greater or less facility and intensity, they are almost constantly present in cases of spastic residual hemiplegia. The neck reflexes are the most marked. Rotation of the head so that the face looks towards the paralysed side produces an extensor spasm in the affected arm. In detail, this consists of adduction and advancement of the upper arm, extension and full pronation of the forearm and increased flexion of wrist and digits. Rotation of the head so that the face points towards the normal side produces an attitude of increased flexion in the paralysed arm. In detail this consists either of abduction or of adduction at the shoulder, of increased flexion at the elbow, so that in some instances the clenched fist comes to lie against the front of the shoulder, and of increased flexion of wrist and digits. An influence of the neck reflexes on the lower limb was less frequently observed, but when present obeyed the same laws.

The labyrinthine reflexes, produced by changes in the posture of the head in relation to the horizontal plane, were not so well marked, but in the case of the upper limb evidence was obtained of a reinforcing effect on extensor tonus when the head was placed in the maximal position, that is, with face pointing upwards and the head slightly retracted.

In certain subjects, simple head rotation, or variations in head posture in relation to space, failed to reveal the presence either of neck or of labyrinthine reflexes. In these cases the presence of both could nevertheless be detected when the associated reactions were examined in the prone, supine and lateral positions, and with the head in the

median and the two rotated positions. In these various positions the neck and the labyrinthine reflexes combine variously and the resulting reactions are described and analysed.

From all these observations it is concluded that the so-called "associated movements" of hemiplegia are tonic or postural reflex reactions allied to the tonic neck and labyrinthine reflexes of Magnus and de Kleijn. They are best elicited by tonic voluntary activity of the normal limbs, and in these circumstances may be described, following Magnus's nomenclature, as "tonic reflexes arising in the limbs and acting on the limbs." The manner in which they combine and interact with the neck and labyrinthine reflexes confirms the view that they are strictly comparable reactions and belong to a large group of reflex reactions by which muscle tone is regulated and the co-ordination of posture achieved. However, if we consider them as a whole, we find that "associated movements" may result from tonic voluntary contraction in face, neck, trunk and limb muscles and may spread so as to involve all these muscles on the hemiplegic side. While it would be possible to divide these reactions into groups according to their point of origin and seat of response, as indeed we have done in the case of those arising in the limbs and acting on the limbs, no good purpose would be achieved. The point illustrated by associated reactions, whatever their place of origin and seat of response, is that while the tone of a given muscle depends primarily and essentially upon the integrity of its own afferent supply, yet this tone is constantly influenced and modified by impulses arising in proprioceptive end-organs elsewhere in the body. Activated by these deep receptors, the reflex mechanisms situated in the brain-stem achieve the co-ordination of posture. The experimental demonstration of this nervous regulation has been provided by the work of Sherrington, and later and more completely by that of Magnus and his co-workers. In proposing the present interpretation of "associated movements" we are, therefore, simply adding to the already weighty evidence that the processes of reflex co-ordination of movement in man are essentially the same as obtain in the lower mammals, and in man, as in animals, the relative intensity of the various tonic reflexes varies from subject to subject.

In man cortical control of these reflex activities is more complete and far more highly developed, and the lines along which this control has developed are beautifully seen in the records of Sherrington and Leyton's observations on the excitable motor cortex of anthropoids [11]. In hemiplegia this cortical control is more or less completely abolished

over the musculature of one half of the body, with the result that there appear on voluntary motor activities two closely allied phenomena, namely, *spasticity* or a selectively distributed hypertonus, and *postural reactions*, including those known clinically as "associated movements." Their "release" from cortical control results not merely in their exaggerated activity, but also and inevitably in their coarse and ill-adapted character. Not only have they been released from control, but they have also depreciated profoundly in fineness of adjustment and purposive adaptation. If, as we believe, spasticity is physiologically identical with experimentally produced decerebrate rigidity, then the appearance of "associated movements" in hemiplegia is a natural corollary to the development of spasticity. Reasons are given for concluding that Marie and Foix's classification of "syncinésies" includes motor phenomena which cannot rightly be termed "associated." Of these some are voluntary, some phasic and only a certain number tonic and reflex in origin. Therefore the term "associated movement," or to be more accurate "associated reaction," should be limited to the phenomena described in Chapter II, it being understood that this is simply an empirical term used to indicate a particular group of postural reflexes, of which allied groups are also present in cases of hemiplegia.

Appendix.

The recording kymograph employed is an elaboration of that described and figured in an earlier paper [14], and was made by Messrs. C. F. Palmer, the physiological instrument makers. It consists of a standard Sherrington-Starling drum, mounted on a drum stand fitted with two special upright arms, the one having two light grooved pulleys round which runs a thread carrying a writing point, and terminating in a long spiral spring at one end, and at the other connected with one of the five speeds of a large-coned vulcanite pulley which is fitted to the other upright arm. From the vulcanite pulley another thread leads off to the limb or group of muscles under investigation. The excursion of the writing point may be varied in amplitude, as required, according to the groove selected on the pulley. Other adjustments ensure a suitable tension of the spring, and length of the thread leading to the subject, and allow the taking of two simultaneous records.

A third upright arm carries the signal and the time-recording

clock. A drum extension fitting is required for lengthy records. The kymograph is driven by means of a small electric motor.

The graphic recording of reflex movements and postures in man possesses many inherent difficulties. Of these the fixation of the patient during the taking of records is one. Any adventitious change of posture in the trunk, which carries the limb with it, causes an excursion of the writing point and vitiates the record of the movement

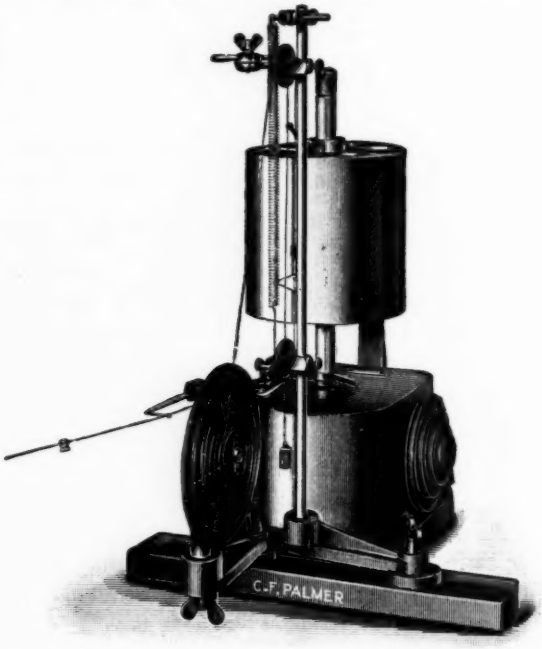


FIG. 11.

under investigation. Further, since in many instances an associated flexion of the elbow in the hemiplegic arm is accompanied by adduction or abduction, protraction or retraction at the shoulder, the graphic record is simply an algebraical summation of movements in as many as three planes at once, and is incapable of analysis. Therefore, not every subject is suited for investigation by this method. Those chosen have been subjects in whom the associated reactions were relatively uncomplicated flexion or extension at the elbow or knee, and who could be relied upon to carry out orders accurately and to lie still.

The subject lies on his back on a hard couch, the hemiplegic arm from which it is desired to take a record has a bracelet fixed round the wrist and is then slung in such a way that free extension and flexion at the elbow can occur when the muscles go into reflex spasm. The thread is then fixed to the dorsum of the wrist distal to the sling by strapping or some other method.

The signalling of stimulation (head rotation or voluntary grasping) is effected by placing the head or hand in circuit with the signal, so that contact is made only during head movement or during grasping.

Addendum.

While the observations recorded in the foregoing chapters were in process of preparation for publication, the writer's attention was drawn by Professor Magnus in a private communication to the two papers of Simons on the same subject (*Neurologisches Centralblatt*, 1920, 39, 132, and *Zeitschrift für die gesamte Neurologie uud Psychiatrie*, 1923, 80, 499). The latter of these, which contains the full account of Simons' observations, only reached this country when the present paper was completed (March, 1923). It has not, therefore, been possible to do complete justice to Simons' work in the body of the paper. In respect of tonic neck reflexes and their influence on associated reactions it is clear that almost all the observations recorded here have been anticipated by Simons, who has illustrated his work by a series of beautiful photographs. His remarks upon the methods of eliciting tonic neck reflexes, their variations in intensity from day to day in a given subject, and from subject to subject, are in complete accord with the present writer's experience. In respect of the lower limbs, Simons has been able to demonstrate more fully developed neck reflexes than has been found possible from the clinical material available for the present observations. It is clear that cases of cerebral diplegia and of hemiplegia of fairly recent origin in young adults are the material from which the most striking results in this direction are to be anticipated. Simons has not succeeded in demonstrating labyrinthine influence on tone, and concludes that this cannot be revealed in man by the methods adequate for the purpose in the case of animals. Yet it is nowhere clear that he has taken the steps necessary to demonstrate labyrinthine reflexes. He has concerned himself exclusively with the effects on limb tonus and on associated reactions of variations in the relation of the head to the trunk. If the associated reactions be examined with the patient in

the supine, prone, right and left lateral positions the influence of the labyrinth can be determined even in the relatively unfavourable clinical material which forms the basis of the present observations. Further, if in each of these four positions head rotation be carried out, it is possible to reveal an interaction of labyrinthine and neck reflexes. On this point, therefore, Simons' work needs amplification.

In addition to the study of neck reflexes in cases presenting pyramidal lesions, Simons has studied a large number of cases presenting one or other of the extrapyramidal syndromes, and has been uniformly unable to demonstrate tonic neck reflexes. The observation is important as emphasizing the fundamental physiological distinction between the spasticity of pyramidal tract lesions and the rigidity of extrapyramidal origin.

He has also been able to demontrate tonic neck reflexes in three cases of high (cervical) spinal lesion. This observation is also of considerable interest. As the present writer has pointed out in the papers referred to in the preceding chapters, the spasticity in the lower limbs in cases of paraplegia in extension is physiologically identical with experimentally produced decerebrate rigidity. It is, however, difficult to understand how a spinal lesion can produce a phenomenon truly akin to this condition. If, as Simons' observations indicate, spinal lesions suffice to produce tonic reflex reactions so closely allied to decerebrate rigidity as are the tonic neck reflexes, then there can be no insuperable obstacle to the view that a form of tonic reflex activity physiologically identical with decerebrate rigidity can result from a lesion at the same anatomical level of the nervous system. It must be stated, however, that Simons does not deal at any length with these or other theoretical considerations, but is primarily concerned to record the facts of observation.

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THE OCULOMOTOR NUCLEUS OF *TARSIUS* AND *NYCTICEBUS*.

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THE researches of Elliot Smith [2] [3] [4] have shown the nature of the cortical changes which are brought about as the result *inter alia* of the enhanced powers of vision developed as a result of the adoption of the arboreal life. He has called attention to the fact that examples of the menotyphlous insectivora lend themselves to comparison as illustrations of these changes, and has described the differences between the brain of the jumping-shrew, *macroscelides*, and the tree-shrew, *tupaia*. "In the tree-shrew," he says, "the importance of the sense of smell is diminished and those of vision, touch, and hearing greatly enhanced. The further emphasizing of these adaptations brought the primates into existence. Among the prosimiæ the reduction of the size of the nose in one group, the tarsioidea, allows the eyes to come to the front of the face so that the fields of vision overlap. The enormous enhancement of the importance of vision which is thus effected leads to the sudden expansion of the cortical area for vision and its further specialization in structure. The sense of sight now completely supplants that of smell as the dominant guide to the animal, and the alteration of the position of the eyes enables the animal to look forward, both in the literal and in the metaphorical senses of the expression" ([4], p. 185).

Brouwer [1], in a clinico-anatomical investigation of the localization of the cell groups comprising the oculomotor nucleus in man, combined with a phylogenetic study embracing representatives of many orders, has been able to deduce certain important principles of general interest relating to the evolution of the oculomotor nucleus. The changes in this structure, it is interesting to note, run parallel with those already referred to in the evolution of the cortex. The most outstanding deduction concerns the relation found to exist between the development of the large-celled median nucleus of Perlia, and the

degree of approximation of the two eyes to one another. Brouwer's conclusion is, that these cells appear phylogenetically when the position of the eyes in the head is such as to render convergence possible (op. cit., p. 189). This point is in itself presumptive evidence that this nucleus sends its axones to the internal recti muscles, which effect the convergence developed coincidently with the appearance of the nucleus. Recently Zweig [12] has, by studying other animals than those chosen by Brouwer, confirmed the general truth of this statement.

Brouwer's series suggested further, that the small-celled Edinger-Westphal nucleus, though forming a median cell group in lower forms (e.g., marsupialia, edentata, rodentia, carnivora), becomes split into two nuclei in the anthropoidea.

At the suggestion of Professor Elliot Smith I have recently investigated the relationship of the oculomotor nucleus to the median plane in two important and not distantly related prosimiæ, the spectral tarsier, *Tarsius spectrum*, and the slow loris, *Nycticebus tardigradus*, in order to correlate the structure of the oculomotor nucleus with the cortical development. The material consisted of two specimens of tarsius and one of nycticebus which were stained in paracarmine. One of the tarsius specimens was cut in horizontal serial sections. The remaining tarsius brain-stem and the nycticebus specimen were cut in transverse series. It is a pleasure to record my thanks to Professor Elliot Smith not only for this material, but for the suggestion to undertake the work and for his assistance throughout the research.

The Oculomotor Nucleus of Tarsius spectrum.

As would be expected from an examination of the size of the eyes the visual connections in tarsius are extremely large. Fig. 1 shows the optic chiasma, optic tracts and lateral geniculate body, and the dorsal view (fig. 2) illustrates the enormous size of the superior colliculus.

An examination of the oculomotor nucleus in the sections shows that the large-celled and small-celled moieties may be clearly differentiated the one from the other. The large cells form two prominent groups on each side of the median plane (fig. 3). Lying between these main groups are many large cells situated ventrally, which are scattered over an area including the median plane (figs. 3 and 4). These cells form the central nucleus of Perlia. Though clearly present this group has not the great development found in the higher

apes and man, where the Perlia nucleus not only connects together the two lateral nuclei but extends cranially in the median plane between and separate from these groups (c.f. Brouwer's figures reproduced in fig. 7).

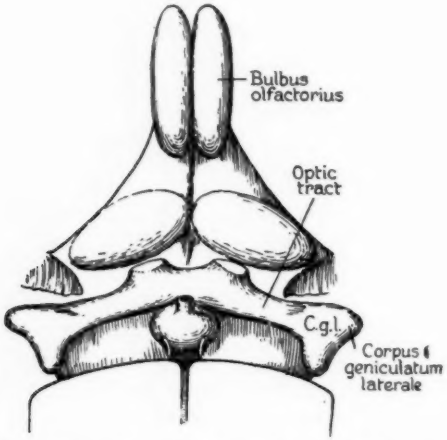

FIG. 1.—Ventral aspect of part of the brain of tarsius.

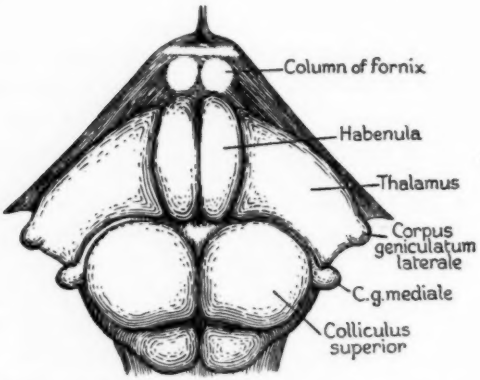

FIG. 2—Dorsal aspect of mid-brain and thalamus of tarsius.

The smaller cells of the oculomotor nucleus form a separate nuclear mass which lies dorsal to the cranial half of the large-celled groups. They stretch across the median plane, so that the division into right

and left portions, which is to be seen in the ape and man (fig. 7) is absent in tarsius, although the cells extend to a considerable distance on each side dorsal to the position occupied by the lateral groups of large cells (fig. 3).

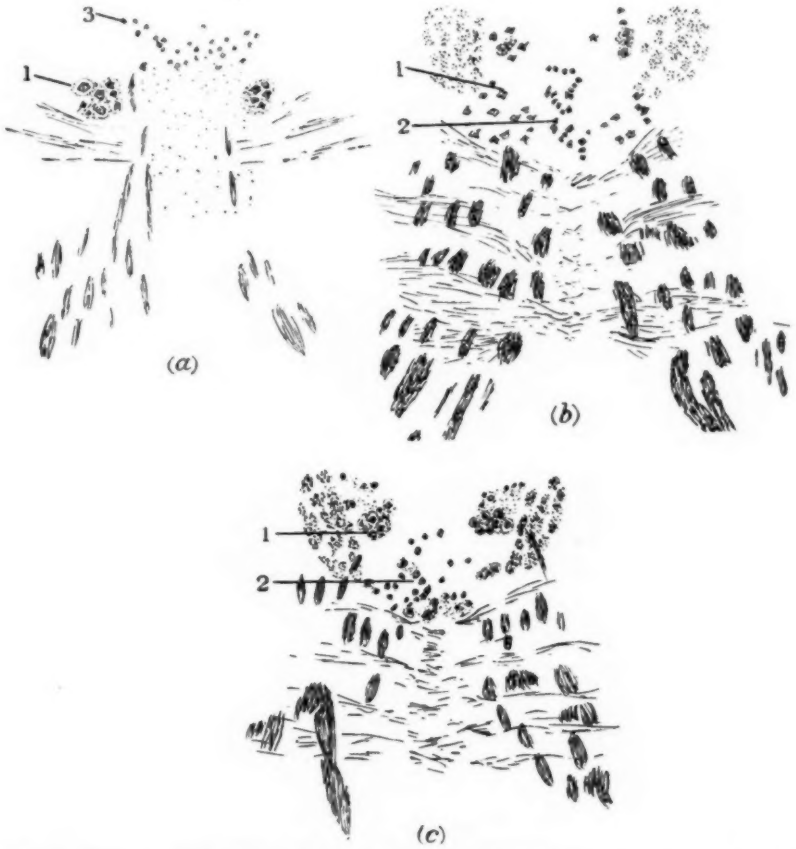

FIG. 3.—Series of transverse sections of oculomotor nucleus of tarsius: (*a*) cranial end; (*b*) middle: (*c*) posterior end. (1, lateral nucleus; 2, nucleus of convergence; 3, Edinger-Westphal nucleus.)

THE OCULOMOTOR NUCLEUS OF NYCTICEBUS.

In this larger brain the relationship of the cell groups to the median plane is revealed with diagrammatic clearness. The large-celled central nucleus of Perlia is beautifully defined (fig. 5).

The relationships of this nucleus are essentially those found in tarsius; it does not attain to the dimensions found in the higher apes and man. The small cells, as in tarsius, here also form a single group which occupies the median line. The illustration (fig. 6) clearly shows

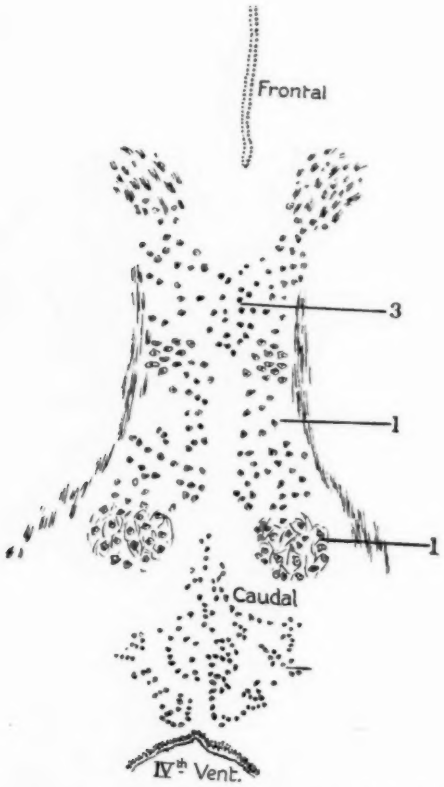

FIG. 4.—Horizontal section of oculomotor nucleus of tarsius. (1, lateral nucleus; 2, nucleus of convergence; 3, Edinger-Westphal nucleus.)

the criteria to be relied upon in the differentiation of these cells from the remaining groups of the oculomotor nucleus. The Edinger-Westphal cells are smaller and less intensely strained than the other cells, and lie closer to the aqueduct of Sylvius (cp. Brouwer, op. cit., p. 171). They are also less distinctly multipolar than the large cells and, as in tarsius, they lie dorsal to the cranial part of the large-celled nucleus.

Discussion.

The reduction of the face has occurred to such an extent in both nycticebus and tarsius that the eyes have become approximated to one another and the fields of vision of the two eyes overlap. This reduction of the face would also render convergence possible, and in support of the contentions of Brouwer the central nucleus of Perlia is to be found in both these forms. The scheme, which has been constructed (fig. 7) to include the oculomotor nucleus of these animals,

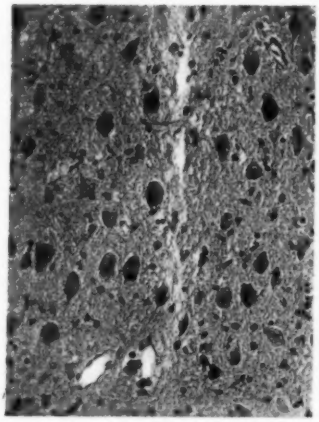

Fig. 5.

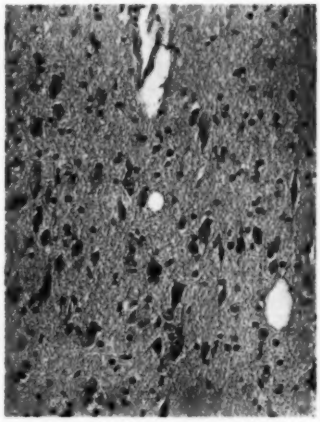

Fig. 6.

Fig. 5.—Photograph of nucleus of Perlia in nycticebus. The slits indicate the median plane.
Fig. 6.—Edinger-Westphal nucleus of nycticebus. The slit indicates the site of the median plane.

clearly demonstrates the truth of this relationship. The variations of the small-celled group are also shown in this scheme, but the interpretation of the results presents grave difficulties. The all-important question of the function of this group is still *sub judice*, and is at present the subject of investigation on the part of the Dutch neurological schools. Moreover, Zweig [12] has shown that the grouping of these cells is not so simple as has been supposed. If the view of Bernheimer were correct, that these cells control the ciliary muscle and sphincter action of the pupil, the scheme drawn up would suggest that the grouping of the small cells has a definite relationship to the development of increased powers of accommodation.

In all forms below the monkeys, as the present investigation confirms, the Edinger-Westphal group is a median nucleus. The bilateral arrangement of these small cells in higher forms suggests that the division into right and left parts is to be associated with the development of the power of accommodation of the two eyes so that they may independently focus a given object, even if it is not equidistant from the two eyes, upon corresponding points of the two retinæ. If this explanation proves to be correct as the result of further investigation upon the function of the Edinger-Westphal nucleus, tarsius and

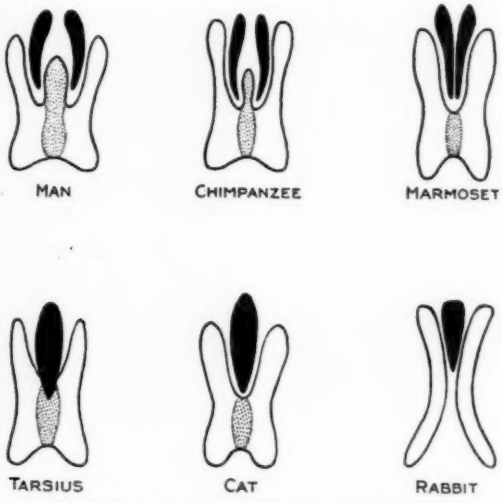

FIG. 7.—Scheme of oculomotor nuclei in various mammals, all except tarsius after Brouwer. Nycticebus would occupy a position immediately below tarsius. (Edinger-Westphal nucleus is represented in black; nucleus of convergence is stippled.)

nycticebus must be placed below the monkeys in the scheme illustrating phylogenetic phases of development of the oculomotor nucleus (fig. 7). The size of the nucleus of convergence is in harmony with this conclusion, for it is much smaller than is the case in the higher apes and man.

Fortunately, however, this is not the only evidence which is to be relied upon in this case. In tarsius, in which the visual apparatus has attained a much greater degree of development than in nycticebus, no macula lutea is to be found. Elliot Smith [4] records that Le Gros Clark, while cautiously refraining from denying its presence, has been

unable to locate a macula lutea either by the ophthalmoscope in the living animal or by direct examination of the retina after opening the eye in the dead; and also that Woollard has failed to identify it in microscopic preparations. These investigations "make it practically certain that in tarsius the distinctive feature of the retina of the anthropoidea (among mammals) is lacking. In this respect tarsius agrees with the lemurs and differs from all monkeys" (op. cit, p. 185).

Moreover, Woollard in an examination of the optic tract could not find non-decussating fibres (op. cit., p. 185). Only degeneration experiments, which are in this instance impossible to carry out, can provide definite evidence on this point. It is likely, however, from the evidence available, that the crossing fibres are comparatively few compared with their number in higher forms. Wilfred Harris [5] believes that the acquisition of the power of conjugate deviation of the eyes and the development of the semi-decussation of the optic tract synchronize with one another. Examination of the movements of the eyes of animals and an investigation by degeneration methods of the proportion of crossed to direct fibres in the optic tract, has convinced him that the eyes must be yoked together and isolated movements must be in abeyance in order to produce stereoscopic vision. The evidence set forth in this paper shows that changes have been effected in the oculomotor nucleus which are associated with the development of binocular vision. But the structure of the nucleus combined with the evidence recorded regarding the absence of the macula lutea, and the probability that relatively few fibres fail to decussate in the optic chiasma, would suggest that tarsius has not attained the stereoscopic vision which is possessed by apes and man. This conclusion harmonizes with that of Treacher Collins [9], who in his Bowman Lecture points out that "no mammals below monkeys have a capacity of distinguishing detail such as is associated with the presence of a fovea centralis," although there is evidence to show "that in the carnivora there is an area centralis in the retina more acutely sensitive to form than the periphery" (p. 29). In summarizing the stages of progressive development of binocular vision, Parsons [7] refers to the evidence of Harris (op. cit.) on this point, and concludes that it seems probable that the cat has stereoscopic vision, and that this is associated with the prehension of the prey by the fore-limbs" (p. 107). Be that as it may, there can be no doubt that in monkeys, as Parsons also states, a distinct advance is made on lower forms, as is shown by the greater range and variety of conjugate movements of the eye and by the development of a true

fovea. It is certain that this stage of development is not attained by tarsius and nycticebus.

It is interesting to note that Riddoch [8] has brought forward clinical evidence which illustrates the true nature of stereoscopic as compared with binocular vision. Riddoch's patient was unable to localize the distance of an object from him, and he could not appreciate the depth and thickness of objects notwithstanding a perfect consciousness of light and shade (p. 47). Riddoch (op. cit., p. 18) has also shown that in recovery of vision after occipital lobe lesions perception of movement precedes that of the moving object, and that the recovery of movement vision begins at the periphery. These conditions probably represent reversions to phylogenetic phases in the evolution of visual perception. The phases of development have been called panoramic, binocular, and stereoscopic respectively; but it must always be borne in mind that one merges into the other. In the transition from panoramic to binocular vision recession of the face with consequent development of the power of convergence is the main factor. The attainment of stereoscopic vision is accompanied by the development of an increased range and variety of the conjugate movement of the eyes, and by the development of a macula lutea in which each foveal cone becomes connected with a single bipolar cell which raises discriminative capacity (Parsons, p. 109). It must not be forgotten that the increased usefulness of the hands would contribute materially to visual experience in regard to the estimation of size and shape. Moreover increased skill in handling small objects must be accompanied by the development of considerable acuity of vision. Nycticebus, like the lemurs (Treacher Collins, op. cit., p. 43), has probably not developed a fovea centralis because it makes use of its mouth in grasping its food to a much greater extent than monkeys (Wood Jones [10], p. 87), or perhaps it would be more logically expressed by the statement that it uses its mouth because it has not yet acquired sufficiently exact visual control to guide its hands with precision. Tarsius makes more use of its hands, but the lack of extensive conjugate movements of the eyes has to a considerable extent been made good by the increased range of movement of the head. This substitution of a gross movement of the eyes and head for the delicately co-ordinated conjugate movements of the eyeballs has probably been a factor in retarding the development of acute form-sense in tarsius. In other respects tarsius exhibits "an over-development of and an exaggerated reliance upon those specializations of vision and its cerebral instruments which were responsible for

the differentiation of the tarsioidea from the lemuroidea and gave impetus to those developments which produced the anthropoidea from one of the tarsioid families" (Elliot Smith [3], p. 466). In becoming a nocturnal animal to secure its safety tarsius lost all opportunity of developing the specialized area at the fovea consisting of a close congregation of cones, the threshold response of which is high. It seems probable that the central stock leading to the anthropoidea attained its supremacy because, as the nose receded and binocular vision with convergence was developed, it acquired synchronously and in due proportion movements of the head and conjugate movements of the eyes (to increase the range of vision which would otherwise be less in the binocular than in the panoramic stage), and an increased range of movement of the fore-limbs.

SUMMARY.

The oculomotor nuclei of *Tarsius spectrum* and *Nycticebus tardigradus* exhibit the presence of a central nucleus of Perlia which is smaller than in the anthropoidea. The presence of this nucleus in these forms accords with the conclusion of Brouwer that the median large-celled nucleus appears phylogentically when the recession of the face allows the approximation and consequent convergence of the eyes. The Edinger-Westphal nucleus is in each case a single nucleus lying dorsal to the large-celled groups in the median plane and extending laterally from it. In the anthropoidea this nucleus is bilateral (Brouwer), and following Bernheimer's theory as to the function of these cells, it is suggested that the power of independently focusing an object on corresponding points of the retinæ, although the object is not equidistant from the two eyes, is to be associated with this bilateral arrangement. The evidence to show that a macula lutea is absent in tarsius is set forth (Elliot Smith, Le Gros Clark, Woollard), and it is also concluded that relatively few optic fibres fail to cross in the optic chiasma. These differences from the anthropoidea are believed to indicate the possession by tarsius of a less acute form sense than in higher forms, i.e., stereoscopic vision has not yet been properly attained.

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LETHARGIC ENCEPHALITIS AND HERPES FEBRILIS.

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INTRODUCTION.

THE nature of the infecting agent in encephalitis lethargica is still a matter of interest, though much work has been done towards the solution of the problem

These investigations have also thrown considerable light on the ætiology of many other infectious diseases.

The first researches on the ætiology of encephalitis lethargica (Wiesner, Bernhard) are now of historical interest only. They attributed it to the virus of influenza, especially the polymorphous diplostreptococcus. It was proved afterwards that the ætiology of these two diseases is different, and that this micro-organism is found in mixed infections only. Wiesner inoculated a monkey with positive result, but it was due to an acute non-specific infection.

Strauss, Hirschfeld and Loewe undertook research work on a larger scale. They inoculated monkeys and rabbits intracerebrally, using the emulsified brain substance from fatal cases of the disease, the discharge from the nasopharynx, and the cerebrospinal fluid. They produced constant and specific lesions in the brain, and they also found this infective when injected into other animals. By this means they were able to get a series of passages. Bacteriological examination did not reveal any micro-organism, and the brain emulsion did not lose its virulence by passing through a porcelain filter. They thus discovered that the virus is a filtrable one, and belongs to the ultramicroscopic group. They succeeded later in growing, under anaerobic conditions on a transudate, very small round bodies which stained with the greatest difficulty by Giemsa stain. These when injected into a rabbit caused a specific infection; with these cultures they obtained a high percentage of positive results.

European investigators have been less fortunate, but McIntosh and Turnbull inoculated a monkey subdurally with an infected brain

emulsion with a positive result; when the monkey died two months later there were typical changes in its nervous system.

The experimental difficulties in research work on this subject were first shown by Levaditi [2]. He made thirty inoculations into the brain and peritoneum of nineteen rabbits, thirteen monkeys and eight guinea-pigs. The infecting material was taken from sixteen cases proved clinically and by microscopic examination to suffer from the disease. Brain emulsion was inoculated ten times, blood three times, cerebrospinal fluid twice, saliva once and discharge from the nasopharynx once. The whole series of experiments produced only two positive results and one doubtful one. Levaditi concluded that it was difficult to reproduce the disease of the Paris epidemic of 1919-20 by inoculation into the rabbit and monkey, and that the virus was located in the nervous system.

Doerr [1] was unsuccessful in his first experiments. The infecting material from eleven cases was inoculated into sixteen rabbits, four guinea-pigs, two mice and five cats without any result. Only the twelfth experiment, in which the cerebrospinal fluid was inoculated into a rabbit under the dura mater, gave a positive result.

Kling in Sweden and Ottolenghi in Italy worked on a much smaller scale. They confirmed the researches of Levaditi. Doerr and all other authors agree that the virus of lethargic encephalitis is a filtrable one, and that all attempts at culture have been hitherto unsuccessful.

The virus is inoculable in laboratory animals, especially monkeys and rabbits, not always with the same ease. In some epidemics a higher percentage of positive results is obtained than in others. This is proved by the different rate of mortality and the clinical symptoms of the infected animals, as we shall see in the second part of this paper. The specific pathological lesions are found in all the inoculated animals. The virus is easily preserved in glycerin, but is destroyed by bile, disinfectants and by heating. The result of inoculation depends on the route by which the infected material is introduced; the best method is inoculation into the cornea or under the dura mater. Intravenous, intraperitoneal and subcutaneous inoculations generally give negative results.

It is a curious fact that inoculation into the testicle causes no local changes here, although the virus remains potent for some time (Levaditi).

From our researches we have come to the same conclusions as Levaditi and Doerr. No matter in what way the virus is introduced

into the animal, it always becomes localized in the central nervous system, travelling to it along the nerve trunks. This was proved by Levaditi, who inoculated a rabbit in the eye; twenty-four hours after inoculation the optic nerve was found to be infected, though the watery discharge from the eye was already sterile. The blood and internal organs do not contain the virus, except the liver where we found specific changes, but our work on this matter is not yet completed.

Important contributions to the ætiology of encephalitis lethargica have been made by researches on herpes febrilis. These were begun by Loewenstern in 1914, continued by Blanc and his fellow workers, and by Doerr and Levaditi. The results of their work may be briefly summarized as follows:—

The vesicles of herpes febrilis contain a filtrable virus, infectious to the rabbit and in a lesser degree to the guinea-pig and mouse. Scratching the cornea of a rabbit with a scalpel infected with the contents of a herpetic vesicle produces along the scratch a series of typical vesicles, accompanied by a conjunctivitis and a thick profuse discharge. According to the intensity of the inflammation this may result in a slight opacity of the cornea, or in the loss of the eye. The virus can be transferred from cornea to cornea. No other micro-organisms are found in the discharge from the conjunctival sac. The diluted discharge passed through a porcelain filter retains its infectivity, and when inoculated into the brain of a rabbit it produces all the symptoms of lethargic encephalitis and leads invariably to the death of the animal. Its virulence can be kept up through a series of passages. It is an interesting fact that the contents of herpetic vesicles occurring in various febrile diseases, as herpes genitalis and herpes zoster, produce the same changes in the rabbit. Consequently the viruses of encephalitis lethargica and of herpes febrilis are closely related, if not identical. The contents of a herpetic vesicle introduced under the dura mater cause specific changes in the brain, and a brain emulsion from an infected rabbit produces identical changes in the cornea. In both instances a series of passages is easily obtained. The brain of a rabbit infected from a herpetic vesicle retains its virulence when preserved in glycerin, but this is destroyed by carbolic acid and bile, and by heat. Reciprocal immunity was obtained with both viruses, inoculation of the cornea with the contents of a vesicle from febrile herpes making the rabbit immune to an intradural inoculation of the virus of encephalitis lethargica, and vice versa.

The close relation of these viruses to each other is shown by the

result of inoculation of a rabbit with the saliva of a patient convalescent from encephalitis lethargica. Levaditi found that this produces typical changes in the rabbit. Later, however, it was discovered that the saliva of fifty per cent. of normal people is capable of producing the same changes. A rabbit inoculated with the saliva becomes immune to the inoculation of the virus of encephalitis lethargica.

From these facts Levaditi draws far-going conclusions. He considers that persons capable of infecting rabbits with their saliva are carriers of encephalitis lethargica, or convalescent from it.

Doerr takes a much simpler view; he believes that normal human saliva may contain the virus of herpes febrilis, and that when this is so the persons are carriers of the herpetic not of the encephalitic virus.

In spite of difference in the interpretation of certain points different observers on the whole agree on the fundamental facts. They agree that there exists a virus or a series of viruses closely related to one another, the inoculation of which causes identical changes in the rabbit. They are all filtrable, easily preserved in glycerin, easily destroyed by bile and other agents, show a special affinity for the brain and skin, and are able to produce cross-immunity.

It is curious that these two viruses so closely related to each other show such a great difference in affecting man, sometimes producing encephalitis lethargica, more often herpes febrilis. Doerr thinks that this may be due to a difference in virulence.

Levaditi has attempted to classify these filtrable viruses with a special affinity to tissues of ectodermal origin, especially to the brain, as ectodermic neurotropes. The viruses of rabies, small-pox and acute poliomyelitis probably belong to this group. They differ from each other by the symptoms they produce, which depends on the ectodermal tissue they affect. Their common characteristic lies in their affinity for these tissues only.

It has been shown that the small-pox virus when inoculated subdurally invariably causes death of the animal. By a series of passages its virulence can be increased, till such a virus is still active in dilution of 1 in 1,000,000 after passages extending over nine months (Levaditi). The virus also gives a definite tissue-immunity when inoculated into the rabbit in very small amounts. The blood of the inoculated animal contains no substance that can neutralize the virus, but its brain when mixed with the virus neutralizes it. The brain of an immunized rabbit inoculated with the small-pox speedily destroys the virus; two hours

later the brain contains no trace of the virus, but the brain of a normal rabbit inoculated with the same small-pox virus becomes virulent after twenty-four hours, that is to say, twenty-four hours is required for the virus to develop in the brain of a rabbit. These facts are probably true for the whole group, to which belong the virus of normal saliva that produces specific infections when inoculated into the cornea, the virus of herpes febrilis and that of encephalitis lethargica. The virus of small-pox causes changes in the skin and the cornea, and affects the brain and spinal cord too. That of rabies produces no specific changes in the skin, and when inoculated into the cornea excites no local changes but becomes localized in the brain and spinal cord. The virus of acute poliomyelitis cannot be inoculated through the skin or cornea, and it produces much slighter changes in the mid-brain and hemispheres than in the spinal cord.

There are other infections in man and animals related to herpes febrilis and encephalitis lethargica, the causal agents of which are unknown. As an example we may mention chicken-pox. There are clinical observations which show the possibility of a chicken-pox epidemic originating from a case of herpes febrilis, and certain experiments prove that the cornea of a rabbit may be infected by the contents of the chicken-pox vesicles. We know very little of the ætiology of mumps, but Levaditi thinks its virus may be closely related to that of lethargic encephalitis. Foot-and-mouth disease, in which the lesions are limited to tissues of ectodermal origin and very similar to those of herpes, and the so-called "Bornasche-Krankheit" of horses which resembles encephalitis lethargica, also belong to the same group.

There are a few points of theoretical interest to which we would like to call attention. Calmette and Guerin found that if one side of a rabbit be shaved and the small-pox virus introduced intravenously, only the shaved side develops the disease. The cause of this is unknown; according to Levaditi there is after shaving an intense proliferation of the superficial layers of the skin in the neighbourhood of the hair follicles, and these young proliferating epithelial cells are a suitable soil on which the small-pox virus may develop. It was shown later that small-pox develops easily on young tissues of ectodermal origin, as cancerous growths of mice and infectious epithelial tumours of fowls.

The ætiology of herpes febrilis, in the light of these new investigations, seemed to us important enough to warrant further experimental investigation.

Herpes febrilis until lately was regarded as an innocent infection

of the skin, appearing either by itself or associated with some acute or chronic infectious disease, as pneumonia, acute cerebrospinal fever or tabes dorsalis, but we know now that it is capable of affecting seriously the nervous system of the rabbit and leading to its death. Our aim has been to determine exactly the pathological and topographical changes caused by the infection. We have also tried to produce in rabbits encephalitis lethargica in order to compare, from the clinical and anatomical points of view, the changes caused by it with those due to herpes febrilis.

Encephalitis Herpetica.

The infecting material was obtained from idiopathic herpes and from herpes associated with cerebrospinal fever and scrofulosis. The inoculations were made through the eye, the cornea being lightly scratched, as in vaccination, with a scalpel. The skin of the patient suffering from herpes was cleaned with ether, the vesicles pricked and the infective material carried by the scalpel to the damaged cornea and rubbed in with some flat instrument. Some of the infective material was often left in the conjunctival sac. All the experiments gave positive results. As a rule, on the third day the cornea became opaque and a thick white purulent discharge poured from the eye. The course of the disease was either acute or chronic.

Acute form.—The general symptoms develop five or seven days after inoculation and death supervenes within a few hours.

Rabbit No. 9, inoculated on March 3, 1922, in the left eye with the contents of a vesicle of herpes febrilis from a case of cerebrospinal fever. On the third day there was a thick purulent discharge from the left eye and some from the right eye too. A week later the animal died in convulsions with typical circus movements.

In the *chronic form* the symptoms develop slowly. The local eye changes diminish gradually and after a few days the animal recovers completely or almost so, but some time later the symptoms reappear.

Rabbit No. 1, inoculated into both eyes December 3, 1921, with the contents of a herpetic vesicle from the ear of a tubercular child; three days later vesicles developed on both eyes, the conjunctivæ were swollen and a thick purulent discharge poured from both eyes, the bacteriological examination of which proved negative. On December 20 both cornea were opaque but there were no vesicles. The left fore limb was paretic and in running the animal deviated towards the right. Those symptoms disappeared and the rabbit seemed well until the middle of January, 1922. Its temperature was not

raised. On January 15 temperature rose to 38°; the head was turned to the right, with the occiput towards the left shoulder, and this forced position persisted in spite of correction. The position of trunk and limbs at rest was normal. In running the limbs were set widely apart, the animal deviated towards the right, fell on its flank and rotated on its longitudinal axis. Placed on its legs the head oscillated in the antero-posterior plane, and there was a vertical nystagmus of the eyes. It frequently ran about with the left side of the muzzle touching the floor, and the right side turned upwards. This condition persisted for two weeks. It was then killed by a blow on the back. An emulsion of its brain was inoculated into another rabbit.

In the chronic cases the animal often dies without apparent cause.

Rabbit No. 5, inoculated on February 7, 1922, with the contents of a herpetic vesicle from a case of cerebrospinal fever, did not show any general signs, but the local changes in the eye were typical of herpetic infection. The animal died on March 3, 1922. Its brain showed typical anatomical lesions of the ordinary distribution.

Inoculation under the dura mater.—The same clinical picture is obtained by subdural inoculations: 1 grm. of brain-tissue from the mid-brain of an animal dead of the disease was emulsified in 5 grm. of normal saline and 0·3 grm. injected subdurally.

Rabbit No. 4 was inoculated under the dura mater with a brain emulsion of rabbit No. 3 on January 25, 1922. General symptoms, as stiffness of the jaw, salivation, circus movements and convulsions, appeared six days later and death occurred on the same day.

These experiments show that herpes, whether idiopathic or complicating cerebrospinal fever, is an infectious disease capable of being transmitted by corneal or subdural inoculations to the central nervous system of rabbits, and the brain of an inoculated animal is infective to other animals. The cerebral changes are manifested clinically by a series of nervous symptoms, as unnatural positions of the head, stereotyped circus movements of the body, profuse salivation, stiffness of the jaw, convulsions and paresis. Post-mortem examination of the brain always reveals pathological changes, which, as we will see in the second part of our work, are identical with those due to encephalitis lethargica.

In our researches we have dealt only with idiopathic herpes, and with herpes complicating cerebrospinal fever and scrofulosis. According to Levaditi and Lipschütz, the same results are obtained with herpes complicating pneumonia and herpes zoster. Until now it has been thought that herpes febrilis was a special reaction of the skin to

different infections, and not a disease *sui generis*; that occurring in cerebrospinal fever has been attributed to the meningococcus, which some observers claim to have demonstrated in the vesicles. Recent investigations must make us revise this hypothesis.

One of us was able to observe two cases which throw some light on the question. One patient, a boy aged 7 years, presented all the signs of cerebrospinal fever, viz., headache, vomiting, stiff neck, dilated pupils, Kernig's sign, high temperature with remissions during the day, and a profuse herpetic eruption beginning on the third day of the disease. A lumbar puncture did not, however, confirm the diagnosis. No other disease was found in the internal organs. Seven days later the boy recovered. In this case the general symptoms seem to have been due to the herpetic infection. The other case was a woman, aged 30, who came to the out-patient department complaining of intense headache, vomiting, sore throat and shivering, of three days' duration. On the second day of the disease she complained of giddiness and felt sleepy. Clinical examination revealed a sore throat, enlarged tonsils and a profuse herpetic eruption on the lips, which, according to the patient, appeared on the third day of the disease. The course of the disease was benign. It seems to us that the sleepiness, vomiting and giddiness were not simple manifestations of the angina, and that the herpetic eruption played here an important rôle.

We find in the literature descriptions of febris herpetica which differ from our cases in the fact that the eruption appeared after the fall of the temperature.

Our researches on encephalitis lethargica confirm, on the whole, the observations of Levaditi and Doerr, with some slight differences. Doerr thinks that animals inoculated through the cornea develop the disease more slowly and die two to four days after the appearance of the first symptom, while in animals inoculated under the dura mater death occurs in twenty-four to thirty-six hours after the appearance of symptoms. This statement was not confirmed by us. We did not find any difference in the clinical course of the disease in animals inoculated through the cornea or subdurally. The susceptibility of the animal seems to be more important; in small animals and albinos the disease often runs a very acute course.

Rabbit No. 6, an albino, 600 grm. in weight, was inoculated on March 11, 1922, under the dura mater with a brain emulsion of rabbit No. 2, which had been infected with the contents of a herpetic vesicle by the cornea. It died on the third day without showing symptoms. The post-mortem examination

showed typical changes in the brain, from which we concluded that death was due to the specific infection.

Encephalitis Lethargica (Epidemica).

We employed as infective material cerebrospinal fluid and discharge from the nasopharynx of cases suffering with encephalitis lethargica, and emulsions of the brains of patients dead of this disease. The infective material was introduced into the eye, and under the dura mater of the brain or of the spinal cord.

Fifty-five inoculations gave eighteen positive results (33 per cent.); that is to say, these animals developed clinical symptoms and died. With the cerebrospinal fluid of one case twelve rabbits were inoculated.

The patient, a man, aged 48 years, became ill in April, 1922. At first he complained of general malaise and anorexia. On the third day myoclonic movements of the lips and lower limbs developed. He became excited and anxious, and on the sixth day sleepless by night and day. Bowels and bladder acted with difficulty. He was admitted into hospital on the tenth day of the illness. There was ptosis of both eyes, more marked on the right side; the reactions of the pupils to light and accommodation were diminished, the ocular movements were limited and the patient was excited and wandered. Occasionally he could be roused and then seemed more conscious of his surroundings, but he was less oriented as regards time. His face was mask-like, skin glossy, and there were myoclonic movements of his lips, nostrils and neck. Temperature was slightly raised, pulse 120, respiration 42. Urine contained 0·2 per cent. of albumin. The cerebrospinal fluid was clear, globulin reaction negative, but the Pandy, Weichbrodt and Targowla reactions were positive; albumin 0·16 per cent., sugar 0·7 per cent., and 16 cells per 1 c.mm.

Rabbits 21a and 21b were inoculated in the usual manner into the cornea with the cerebrospinal fluid of this patient, and on the following day the second eye of each rabbit was inoculated with discharge from his nasopharynx. Three weeks later both rabbits appeared quite well, their temperatures were normal and no changes developed in the eyes, except a small white spot on the left eye of rabbit 21a, which had been infected with the nasopharyngeal discharge. On May 15, twenty-six days after inoculation, rabbit 21a showed definite symptoms, as retraction of the head, profuse salivation and seizures in which the hind limbs were extended and the fore limbs and the muscles of the muzzle convulsed. These attacks usually lasted a few minutes and after them the animal ran about in circus movements to the left. Between the attacks the animal seemed dazed, and when immobile stood with its fore limbs widely apart. When running in a straight line it failed

to avoid obstacles, and often hurt its muzzle against the wall. The animal died eighteen hours later. Macroscopically the brain showed some congestion, and microscopically marked inflammatory and degenerative changes, which will be described later, were found in it.

After the death of this patient a brain emulsion of the grey matter of the mid-brain, obtained under strict aseptic conditions, was inoculated into the cornea and under the dura mater of six rabbits. Five animals died, one four days after the inoculation without showing any clinical symptoms. Rabbit No. 25 died two weeks after the inoculation under the dura mater For twelve days it seemed well, but then the temperature rose to 39° for three days, and the animal became dazed, immobile, and lay with its back arched. Three days later the temperature fell to 35° and the animal died. Rabbits 21 and 26 died three weeks later without developing clinical symptoms, and the fifth rabbit died a month after inoculation without clinical symptoms too. In all five rabbits there was marked meningitis and inflammation of the nervous tissues. The sixth rabbit remained well, but when killed six months later its nervous system showed marked inflammatory scarring, which will be described later.

This group of observations shows how very difficult it is to determine the inoculation period, and even to prove clinically that the infection had taken place. The disease may run a most acute course to a fatal termination within four days, or may end in recovery after a protracted course. It may be said that on the whole the acute form lasts two weeks, the chronic form four to six weeks, both terminating fatally. As in the herpetic infections, small sized animals are more susceptible, the disease being more acute in them. The site of inoculation does not seem to have an important influence on the course of the disease: rabbit No. 23 died four days after the inoculation into the eye ; all the other animals were inoculated under the dura mater.

In another series of experiments the cerebrospinal fluid of a woman, aged 42, was used as inoculation material.

On April 10, 1922, she complained of dimness of vision and sleepiness. When awake she was quite conscious. Two weeks later she became sleepless ; during the whole time she did not complain of pain. At the beginning of May she developed myoclonic movements in her left upper limb. When she was admitted to hospital on May 10 her eyes were half-closed, the ocular movements were normal, and there was no nystagmus ; the pupils unequal, the right being larger, their reaction to light was diminished and that to accommodation lost. There were incessant movements of the fingers of the left

upper limb which took the form of scratching the inner side of the thumb or the thenar eminence; sometimes she scratched her head in the same stereotyped way. Those movements ceased during sleep. In the lower limbs there was constant dorsiflexion and extension of both feet, and from time to time slight raising of the whole limb. The tendon reflexes were lively, the skin reflexes diminished. The tension of the muscles at the left elbow was slightly increased (slight stiffness on extension of the joint). The cerebrospinal fluid was clear but under slight tension; the Nonne-Apelt reaction was slightly positive but there was no excess of cells.

0·5 c.cm. of the fluid was injected into two rabbits.

Rabbit No. 34 was inoculated under the dura mater and into the spinal canal; rabbit No. 36 into the right eye. The first rabbit died three and a half months after the inoculation, the second four weeks after it. The first one was a big specimen, the second of small size.

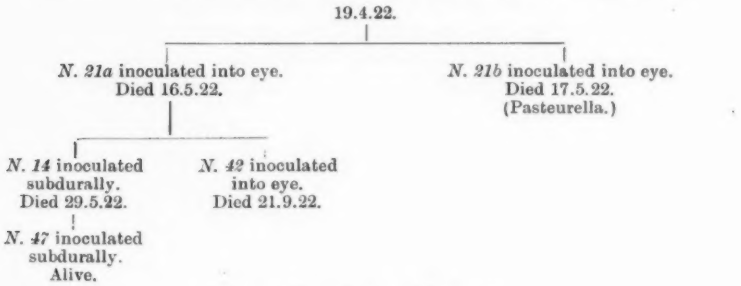
Five days after inoculation rabbit No. 36 showed a slight paresis of the right hind leg, which passed off in a few days. Two weeks later the temperature rose to 40° for a week or so, but dropped to 36° before death. For one day before its death rabbit No. 34 seemed dazed, reeled to the left when running, had marked head retraction and trembled all over.

In a series of inoculations with infective material from other patients the results were much the same. The results were equally positive with inoculations of cerebrospinal fluid, of the discharge from the nasopharynx and of brain emulsion. Anatomical changes were found in all, but clinical symptoms in a certain proportion only. We also noticed that the virulence of the infective material depended less on its source than on the intensity of the disease in the patient.

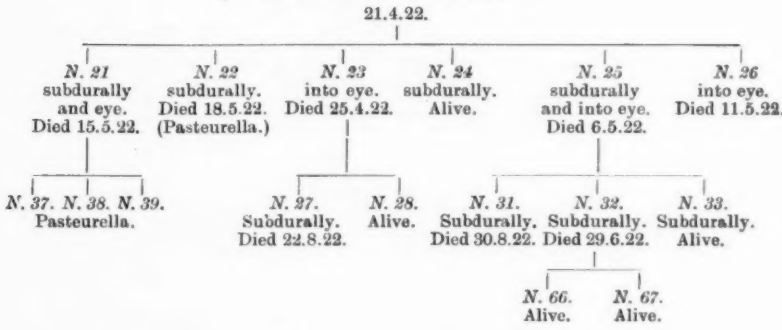
Inoculation of Healthy Rabbits with Brain Emulsions of Rabbits infected with Encephalitis Lethargica.

In this series of experiments we inoculated animals with brain emulsions from other animals who had died from the disease, or had been killed after infection. We are unable to classify the results of these experiments since a secondary infection (pasteurella) destroyed a great number of our animals. We counted only those cases as positive which showed clinical symptoms typical of the disease, and which were free from the pasteurella infection. It is much more difficult to infect rabbits with material taken from other infected rabbits than with material from human patients. The following charts illustrate this clearly.

CEREBROSPINAL FLUID AND DISCHARGE FROM NASOPHARYNX OF PATIENT C.


19.4.22.
N. 21a inoculated into eye. Died 16.5.22.
N. 21b inoculated into eye. Died 17.5.22. (Pasteurella.)
N. 14 inoculated subdurally. Died 29.5.22.
N. 42 inoculated into eye. Died 21.9.22.
N. 47 inoculated subdurally. Alive.

BRAIN EMULSION OF PATIENT C.


21.4.22.
N. 21 subdurally and eye. Died 15.5.22.
N. 22 subdurally. Died 18.5.22. (Pasteurella.)
N. 23 into eye. Died 25.4.22.
N. 24 subdurally. Alive.
N. 25 subdurally and into eye. Died 6.5.22.
N. 26 into eye. Died 11.5.22.
N. 37. N. 38. N. 39. Pasteurella.
N. 27. Subdurally. Died 22.8.22.
N. 28. Alive.
N. 31. Subdurally. Died 30.8.22.
N. 32. Subdurally. Died 29.6.22.
N. 33. Subdurally. Alive.
N. 66. Alive.
N. 67. Alive.

The incubation period is prolonged when the infection is transferred from animal to animal; as an example we may mention rabbit No. 31 which, inoculated subdurally and into the right eye on May 6, with a brain emulsion of rabbit No. 25, remained quite well for four months, during which time there were no signs that infection had taken place. Then the temperature rose to 39·6°, the head turned to the left and downwards, the animal lay on his left flank and when put on his legs executed definite circus movements, the left legs moving on the smaller curve. It frequently rotated on its longitudinal axis, the right side turning round to the left. There was vertical nystagmus, more marked in the right eye. When held up by its ears the body and hind limbs described circular movements in the air and when placed again on the floor oscillatory movements of the head appeared. These symptoms lasted two days. The animal was killed by a blow on the head. Rabbit No. 42, infected with a brain emulsion of rabbit No. 21a, had also a long incubation period (see diagram). There was a slight ulceration on the right cornea and a slight rise of temperature. The animal

died four months later. Its brain showed typical changes. As an example of a more acute course in the same series we may mention rabbit No. 41, which was inoculated subdurally on May 16 with a brain emulsion of rabbit 21a; six days later the temperature rose to 40·8° and the hind legs became paralysed. During the next six days the temperature fell to 36° and the animal died on May 29.

We must therefore conclude that the clinical symptoms of infection by encephalitis lethargica are identical with those of herpetic infection. The local changes in the eyes are, however, much more intense in the herpetic infection; in encephalitis lethargica there may be no reaction, or a slight irritation of the eyes only. Levaditi believes this is due to the greater affinity of the herpetic virus for the skin and designates this property dermotropic; he terms the affinity of the virus of encephalitis lethargica for the brain tissue neurotropic.

There is a great difference between the clinical course of the disease in man and in animals. In the latter the infection is not always accompanied by clinical symptoms and is sometimes detected only by post-mortem examination. It is not known that in man symptoms may be absent when infection is present.

In animals the most common symptoms are abnormal positions of the head, circus movements, nystagmus and oscillatory movements of the head, that is, symptoms of labyrinthine involvement. Siegrist and Stocker have, in fact, observed involvement of the labyrinth and thought it was the cause of the symptoms. Doerr and Schnabel found the same symptoms in animals whether the labyrinths were involved or not. In our series no involvement of the labyrinth was found in the pathological examinations made by Dr. Karbowski. We therefore attribute the symptoms to involvement of the nervous system, and indeed we always found there changes capable of explaining them. Another frequent symptom in animals which is seldom found in man are either general or local convulsions.

We certainly do not agree with Kling, David and Lilienquist, who describe a great similarity between the symptoms in man and animals, these being "spasmodic or catatonic conditions, tremors not unlike the tremor of Parkinson's disease, and convulsions." We never noticed in our series such spasmodic or catatonic symptoms, nor tremor nor myoclonic movements, and convulsions occur very rarely in man.

Symptoms of Parkinson's disease appear in man later, when the disease has lasted for some time. We purposely kept a certain number of rabbits alive in order to see if this complication would arise, but it has

not occurred till now. We have also failed to observe in our rabbits any sleepiness or paralysis of the oculo-motor nerves. We do not think that running into obstacles was due to visual troubles as Doerr and Schnabel believe ; examination of vision and histological examination of the nervous system do not support their view. It was more probably due to the kinetic and static disturbances so frequent in our animals.

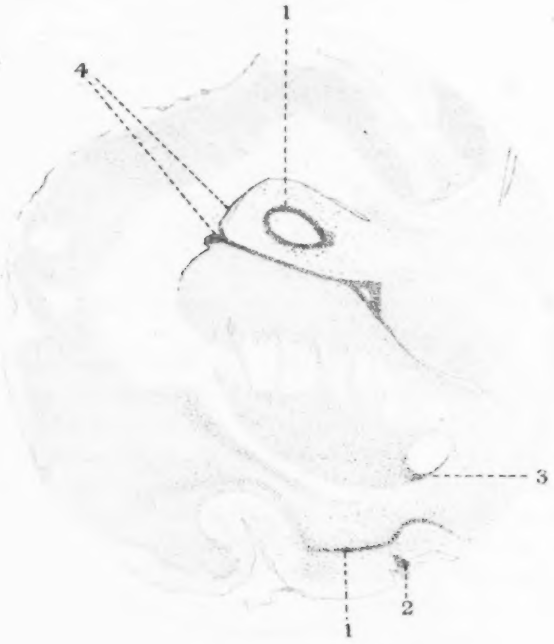


FIG. 1.—Celloidin section stained with thionin. (Zeiss, Oc. 0, Obj. a, 2.) (1) A layer of pyramidal cells in the cornu Ammonis. (2) An inflammatory focus. (3) An inflammatory focus in the lenticular nucleus. (4) Inflammatory infiltration of ependyma and choroid plexus of the lateral ventricle.

Pathological Changes.

The pathological changes are identical in both infections. Although there are three forms of the disease, acute, subacute and chronic, the changes in the brain may be described as either acute or chronic.

Pathological Changes in the Acute Form.

Rabbit No. 25 was inoculated subdurally with a brain emulsion of a patient dead of encephalitis lethargica. Macroscopically the brain showed some slight

congestion. Microscopically there was a well marked infiltration of the pia mater all over the brain, most marked at the base and in the neighbourhood of the optic and oculo-motor nerves, and from here the inflammation penetrated into the brain tissue. The pia mater over the cerebellum was only slightly infiltrated. In some places the blood-vessels showed perivascular infiltration, chiefly in the superficial layers of the base. In the brain tissue, and principally in the region of the lenticular and caudate nuclei, there were foci of cellular infiltration which was most marked on the ventricular side of the caudate

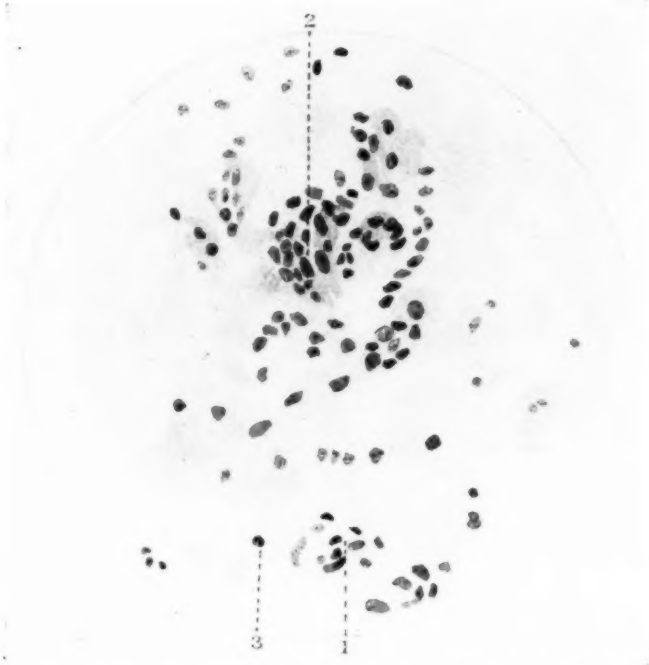


FIG. 2.—Inflammatory focus in the lenticular nucleus. (Zeiss, Oc. 2, Obj. DD.) (1) A large mononuclear cell. (2) A group of large mononuclear cells. (3) A lymphocyte.

nucleus (fig. 1). No inflammation was found in the cerebellum, pons or medulla oblongata. The infiltration consisted of mononuclear elements, large mononuclear cells and lymphocytes (fig 2). Degenerative changes, in the form of chromatolysis, were present throughout the nervous system; it was less marked in the cortical cells than in those of the caudate and lenticular nuclei. The Purkinje cells in the cerebellum had undergone marked chromatolysis; some of them had disappeared completely and were replaced by neuroglia, or only traces of them remained. The small cells of the zona molecularis

showed the degenerative changes described by Simchowitch; the nucleus was contracted, the chromatin granules arranged on its periphery, the protoplasm dissolved gradually and finally surrounded the nucleus as a small zone, separated from it by a lighter one. In the last stages of degeneration the cells come to resemble plasma cells. We found similar changes in the locus niger of Soemmering, and marked chromatolysis in the cells of Deiters' nuclei and in the dentate nuclei of the cerebellum.

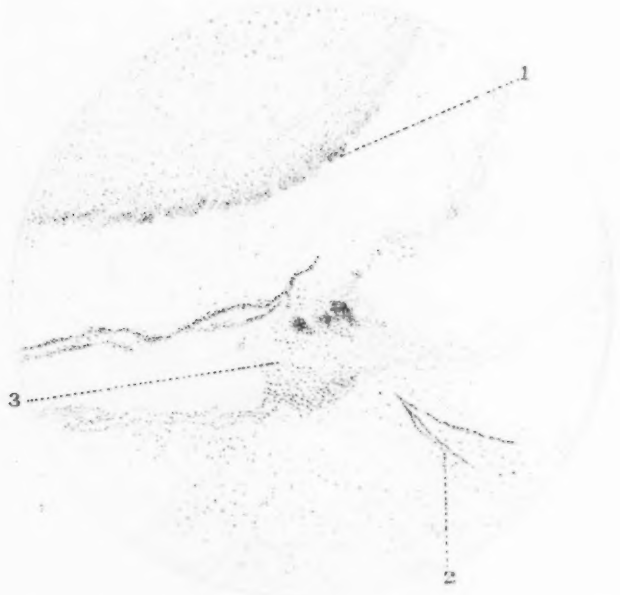


FIG. 3.—(Zeiss, Oc. 0, Obj. aa). (1) Cortex. (2) A patch of inflammatory infiltration. (3) An inflammatory focus between the optic thalamus and the cortex.

The disease ran a more acute course in a rabbit inoculated on April 1 subdurally and into the right eye with a brain emulsion from another rabbit infected with encephalitis lethargica. It died eight days later without showing any clinical symptoms. In the pia mater over the base of the brain, and in a lesser degree in the choroid plexus of the third ventricle, there was a cellular infiltration. The blood-vessels were only slightly infiltrated and the pia mater was hardly infiltrated at all except over the fissure separating the cerebellum from the medulla oblongata where we found marked infiltration round the blood-vessels. Inflammatory changes were on the whole slight, but the degenerative lesions were very striking. There was marked chromatolysis of

the cells of the optic thalamus, in those of the nuclei of the floor of the fourth ventricle and even in the anterior horns of the cord. Some cells had disappeared completely. The zona molecularis of the cerebellum showed the same changes as in rabbit No. 25. In the cells of Deiters' nuclei the Nissl's corpuscles were completely disintegrated, the nucleus was swollen and situated excentrically, in places the protoplasm did not stain at all, and of some cells only traces remained.

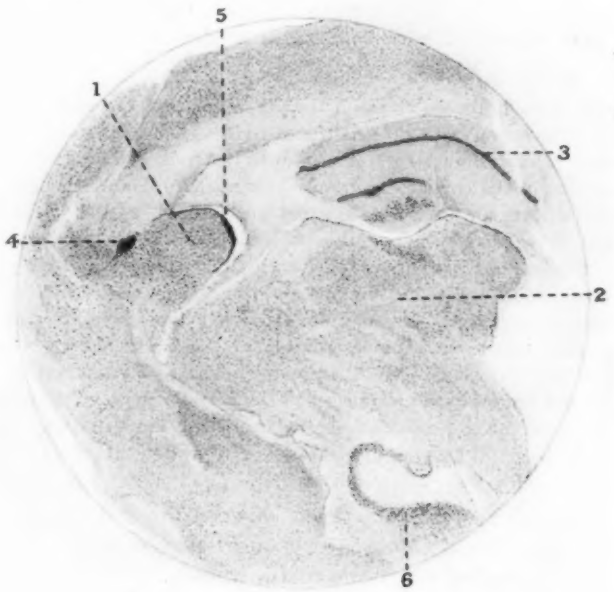


FIG. 4.—(Zeiss, Oc. 0, Obj. a2). (1) Nucleus caudatus. (2) Optic thalamus. (3) A layer of pyramidal cells in the cornu Ammonis. (4) An inflammatory focus. (5) The lateral ventricle. (6) The cornu Ammonis.

These pathological changes were typical. The mononuclear infiltration was a constant feature, even in the most acute cases that proved fatal within two days.

Rabbit No. 6: Small size, albino. Inoculated on March 11 under the dura mater with brain emulsion from rabbit No. 2, died March 13. In spite of the short duration there were typical changes in the usual regions: in the base of the brain, in the periphery of the nucleus caudatus, in the wall of the lateral ventricle and in the region of stratum zonale of the optic thalamus. The infiltration consisted

of mononuclear elements, except at the base of the brain where a few polynuclear cells were found. We may say that the mononuclear infiltration was typical for both infections. Our observations differ in this from Levaditi and Harvier, who found mononuclear infiltration in the chronic forms and polynuclear cells in the acute cases. Our observations seem to confirm the views of Bergel who states that some bacteria of a lipoid nature, as Koch's bacillus, cause a mononucleocytosis.

We have described rabbit No. 21a as an example of a subacute infection (p. 57).

Examining its brain we found in the pia mater over the base of the brain a marked infiltration which penetrated into the brain tissue for a few millimetres. There were small foci of cellular infiltration scattered about, most numerous in the caudate and lenticular nuclei. The walls of the blood-vessels were thickened, the adventitia had proliferated, and the lumen of the vessels was in some places completely occluded. There was marked perivascular infiltration ("manchons perivasculaires"), especially in the above mentioned nuclei. Between the vessels the tissues were infiltrated with mononuclear cells, plasma cells and elongated cells resembling Stäbchenzellen, and by granules resulting from destruction of the cells. There was marked proliferation of neuroglia. No inflammatory changes were found in the cerebellum. A few neurophages were seen in the cortical cells. The degenerative changes were similar to those described above; they were most marked in the Purkinje cells and in Deiters' nuclei and least evident in the cortical cells. The ocular muscles were also infiltrated.

Consequently the only difference between the last observation and the two others was the presence of neurophages and plasma cells, and the thickening of the walls of the vessels.

Pathological Changes in the Chronic Form.

Inflammatory changes.—We may mention as an example rabbit No. 1 which had been inoculated into the eye with the contents of a herpetic vesicle.

The inflammatory changes were discrete. There was a slight infiltration of the pia mater over the base and convexity of the brain, seen clearly in a transverse section through its anterior part. A few inflammatory cells were also found in the ependyma of the lateral ventricles. There were scattered inflammatory foci in the caudate and lenticular nuclei and in the septum pellucidum. In a more posterior transverse section (figs. 2 and 5) a large inflammatory focus was seen in the angle between the caudate nucleus and the cortex, and a smaller one in the nucleus amygdalæ. There was a hæmorrhage

and some infiltration on the surface of the thalamus and in the pia mater over the cerebral peduncles: the locus niger of Soemmering contained small inflammatory foci and there was some infiltration of the blood-vessels in the caudate and lenticular nuclei. The infiltration consisted of mononuclear elements (lymphocytes and here and there plasma cells). (Fig. 6.)

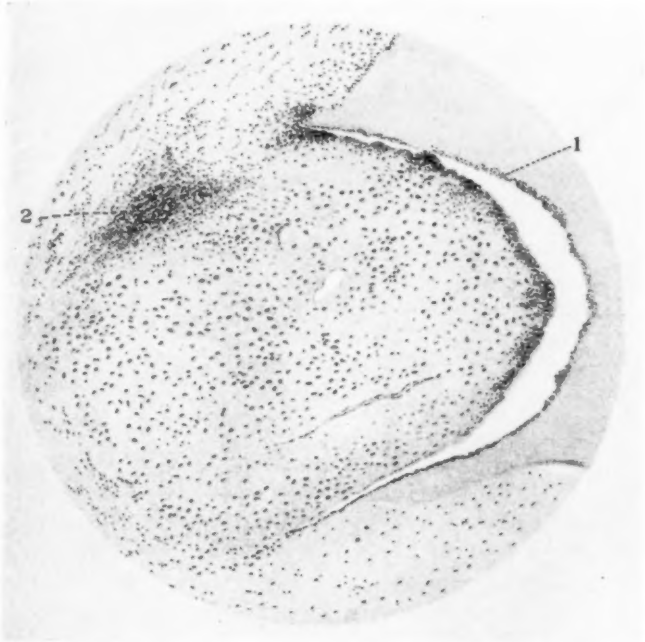


FIG. 5.—An inflammatory focus in the caudate nucleus. (Zeiss, Oc. 2, Obj. aa.)
(1) Ependyma of the lateral ventricle. (2) An inflammatory focus.

Degenerative changes.—Degenerative changes were very marked in the nerve cells. In the cortical cells we found chromatolysis and vacuoles; the Purkinje cells had partially disappeared; those of the red nuclei stained with difficulty, their nuclei were swollen and they were surrounded by neurophages; the cells of the third nerve nuclei had also undergone chromatolysis.

From this description we see that in the chronic cases there is much less small cell infiltration than in the acute cases, but more proliferation of the connective tissue in the meninges, and in the nervous tissues polyblasts and plasma cells are found. Degenerative changes, on the other hand, were prominent in all of them. In a few rabbits, however,

in which the disease ran an acute course, post-mortem examination revealed the same predominance of degenerative changes.

Rabbit No. 20, albino, 440 grm. weight. Inoculated into the right eye with a brain emulsion of rabbit dead of encephalitis lethargica. It died on the eighth day. There was very slight infiltration in the region of the optic nerves

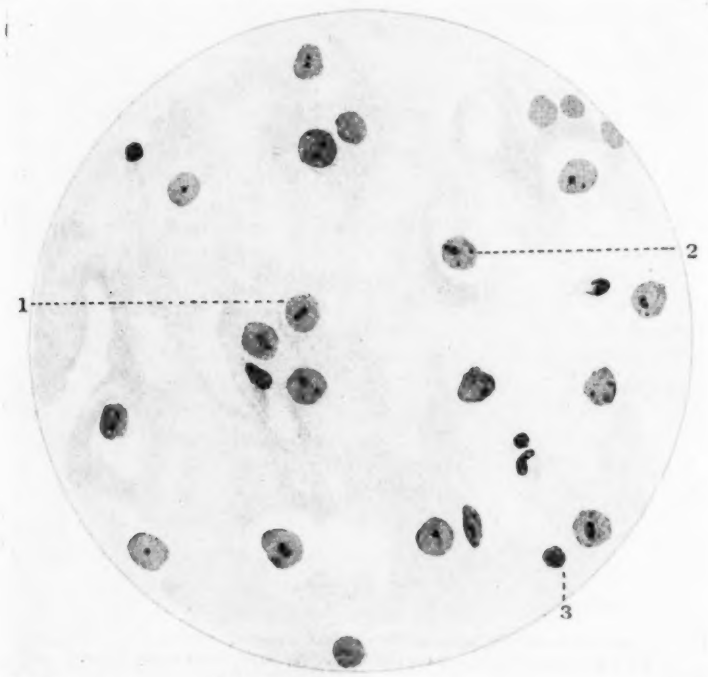


FIG. 6.—The inflammatory focus seen in fig. 5. (Zeiss, Oc. 2, Obj. immersion.)
(1) A large mononuclear cell. (2) A lymphocyte.

and in the medulla oblongata an inflammatory focus, consisting of mononuclear elements surrounded by neuroglia, was present. The degenerative changes were marked and not of the usual type; in the cells of the caudate nucleus and of the cornu Ammonis the protoplasm stained with difficulty, and in some cells only the nuclei, which were large and stained poorly, contained a large spindle-shaped nucleolus with dark well-stained corpuscles at both ends; this appearance suggested a mitosis (fig. 7). In some nuclei there were two such structures, but other nuclei contained several

small corpuscles in addition to the nucleolus. The cells of Purkinje and those of the grey matter in the floor of the fourth ventricle showed beginning chromatolysis.

The brains of rabbits which died without developing clinical symptoms presented post-inflammatory scarring of long standing; such changes were found in all animals killed some time after infection.

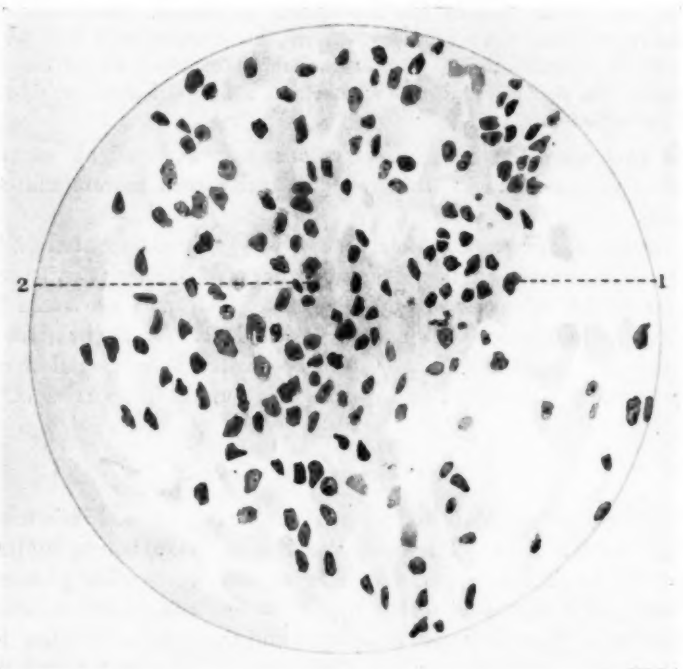


FIG. 7.—The caudate nucleus. (Zeiss, Oc. 2, Obj. immersion.) (1) A nucleus of a nerve cell with its spindle-shaped nucleolus. (2) A nucleus with a spindle-shaped nucleolus and two corpuscles. (3) A neuroglia cell.

Oliver, however, found in 20 per cent. of normal rabbits inflammatory changes of long standing, indicating some previous inflammation of the brain.

The rabbit No. 31 helped to determine the origin of the labyrinthine symptoms so often met in our investigations.

Old post-inflammatory changes were found at the base of the brain, the pia mater being thickened and containing a great amount of fibroblasts and con-

nective tissue; the intima and adventitia of the blood-vessels were proliferated, and here and there in the cortex and thalami there was a mononuclear infiltration of their walls. In one place, on the border of the pia mater and cortex, there were traces of an old inflammatory focus, consisting of fibroblasts, plasma cells and polyblasts. In transverse sections more posteriorly a more intense infiltration of the pia mater over the base was found, especially at the level of the corpora quadrigemina. No inflammatory changes were discovered in the brain tissue, except in the nucleus of the nervus vestibularis and in the tuberculum acusticum. The cells of the nucleus vestibularis were degenerated. Slight changes were also found in the cells of Deiters' nuclei and of the nuclei of the floor of the fourth ventricle, but the cells of the cerebellum, red nuclei and nuclei dentate were not affected.

In this case the inflammatory changes were slight except in the nucleus vestibularis; this explains the circus movements of the animals.

We are at present unable to say why animals so often develop these circus movements and disturbances of static position which are never met in man. It may be that in animals the virus has a selective affinity for the nervus vestibularis as it has for the oculomotor nuclei in man, or it may be due to a special arrangement of the blood-vessels or to some biochemical properties of these nuclei.

Changes in the Liver.

In all our animals infected with either virus we found inflammatory changes in the liver. These consisted of a mononuclear infiltration round the small bile ducts, the inflammatory cells often penetrating between their epithelial cells which were occasionally much proproliferated. The liver was congested and the cells around the blood-vessels were often destroyed. Such changes were not found in the spleen and kidneys. The relation between affections of the grey matter of the brain and diseases of the liver were first pointed out by Wilson, who found that affections of the lenticular nucleus were often accompanied by cirrhosis of the liver. Wilson considered the liver affection as primary, the brain being secondarily affected as result of disturbed metabolism. Our experiments suggest that both organs were affected simultaneously. The livers of patients who have died of encephalitis lethargica contain changes similar to those we found in the rabbits, but as we have not yet been able to examine many human livers, we cannot come to definite conclusions.

Our experimental work on the liver has been only recently undertaken. We have proved, however, that the infiltration of the bile ducts is not merely due to toxins or to disturbance of metabolism, since by injecting animals with an emulsion of liver tissue in the same way as we did with a brain emulsion, we have been able to reproduce the disease, and therefore to show that the virus itself is localized in the liver.

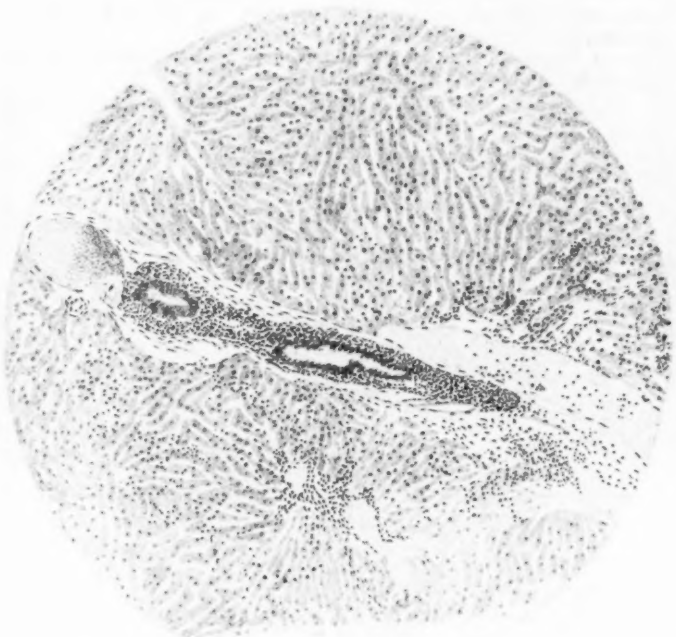


FIG. 8.—(Zeiss, Oc. 2, Obj. aa.) Infiltration of the bile ducts in the liver.

There are many characters common to the infection of man and animals; the infiltration consists of mononuclear cells in both, its localization in the basal ganglia was also similar, and degenerative changes in the cerebellum occur in man as well as in the rabbit. We have been able several times to demonstrate marked degenerative changes in the Purkinje cells in man, though inflammatory changes were

absent. The meninges, however, react differently, since in man their affection plays an important part in the pathological picture. This seems to contradict Levaditi s view of the ectodermotropic nature of the virus, that is to say, its special affinity for the tissues of ectodermal origin. That the liver is also involved is another argument against his hypothesis.

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DYSTROPHIA MYOTONICA (MYOTONIA ATROPHICA).

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I.—INTRODUCTION.
II.—DESCRIPTION OF CASES.
III.—GENERAL DESCRIPTION OF THE DISEASE.
(1) Onset and course.
(2) Myotonia and muscular atrophy.
(3) Cataract.
(4) Other extra-muscular symptoms.
IV.—HEREDO-FAMILIAL FEATURES.
V.—PATHOLOGY.
VI.—CONCLUSIONS.

I.—INTRODUCTION.

THE history of the disease we are about to consider may be said to begin in 1886 with the appearance of Erb's monograph on Thomsen's disease; for although myotonia congenita and myotonia atrophica are distinct conditions, Erb's work, by arousing widespread interest in myotonia in general, led to the publication of a large number of cases of so-called atypical Thomsen's disease and this brought to light the group of cases that now concerns us in which myotonia is associated with atrophy of the muscles.

This curious combination of symptoms was described for the first time by Deleage in 1890; thereafter isolated cases were recorded by Hoffmann, Jolly, Kornhold, Nogues and Sirol, Schultze, Berg, Curschmann, Fürnrohr and others, but no real advance was made until 1909, when Batten and Gibb [4] and Steinert [54] gave independent descriptions of the clinical features of this group and showed that it constituted a distinct and characteristic symptom-complex. Unlike earlier writers, who detected no uniformity in the distribution of the atrophy, these observers found that it was constant in certain positions, namely in the face, where it gave rise to the facies myopathica,

in the muscles of mastication, the sternomastoids, the forearms, and, less often, in the peronei; but whilst they agreed on many points they differed in their conception of the nature of their cases and the sequence of the symptoms, for Steinert maintained that myotonia was the essential and initial symptom, atrophy being merely an incident in the course of Thomsen's disease, whereas Batten gave priority to atrophy, and, holding that myotonia was " merely a symptom," placed his cases in a group amongst the myopathies.

Time has confirmed the general accuracy of their descriptions of the muscular symptoms; but it has also brought into prominence a number of extra-muscular phenomena, some of which, though noticed before, had been regarded as fortuitous, and has brought about a complete change in our conception of the nature of a disease, which, far from being an affection of the muscular system alone, is now known to be a general dystrophic disorder with diverse and widespread manifestations.

This significant change followed closely upon the discovery that cataract was a frequent symptom. In 1911 one of us [16] described a family of thirteen brothers and sisters, of whom five suffered from myotonia atrophica, two with and three without cataract, and two from cataract alone. In the same year accounts of patients with myotonia atrophica and cataract were published by Kennedy and Oberndorf [34] and Ormond [44] and thereafter the number of similar observations increased rapidly. At once the other extra-muscular symptoms, as atrophy of the testicles, baldness, loss of body weight, and the rest, which had hitherto been regarded as more or less accidental, were viewed in a new light. In 1912, Curschmann [8], who was the first to recognize their significance, elevated them to a cardinal position at least equal in importance with myotonia and muscular atrophy in the symptomatology of the disease, and insisted that they must receive full consideration in any discussion on its nature. At the same time he expressed his agreement with Lewandowsky [37], Hirschfeld [27] and Grund [19], who had already in separate papers declared the independence of these cases from Thomsen's disease, and gave his classical description, to which little of material importance has since been added. According to this description the main features of the disease are briefly: Onset between the ages of 20 and 30 years in contrast to the earlier onset of Thomsen's disease; muscular atrophy of peculiar distribution as described by Batten and Steinert, namely facies myopathica with atrophy of the sternomastoids and the muscles of the forearms; myotonia confined to a few muscles and usually present in

the hand-grasps alone; loss of tendon reflexes; extra-muscular symptoms, of which the most frequent are cataract, baldness, atrophy of the testicles and impotence; various vasomotor disturbances, and general atrophy and loss of weight.

At this stage in its history dystrophia myotonica was regarded as a distinct disease characterized by the triad, muscular atrophy of peculiar distribution, myotonia and certain extra-muscular "dystrophic" symptoms.

In recent years, however, its status has changed again, for Fleischer's [12] investigations into the family history of patients presenting this combination of symptoms have shown that this syndrome is but one aspect of an heredo-familial disease whose presence may be expressed in divers ways.

The changes that have occurred in the status of the disease from time to time are reflected in the names it has borne. The early designation, "Thomsen's disease with muscular atrophy," is a reminder of a period when myotonia and Thomsen's disease were synonymous and when any patient with myotonia, though deviating in any respect from Erb's classical description, was described as an atypical case of Thomsen's disease. In 1901 Rossolimo [48] proposed the name "myotonia atrophica" for those cases in which atrophy was supposed to have supervened in the course of Thomsen's disease, and this name has been retained in this country, although the two diseases are now known to be separate. In recent years the name proposed by Curschmann—dystrophia myotonica—has been adopted, because it emphasizes the dystrophic phenomena; but it is certain that finality in nomenclature has not been reached, because a name is still required which will designate the heredo-familial disease of which the syndrome dystrophia myotonica is a part. The name proposed by Naegeli [41]—"pluriglanduläre Erkrankung innersekretorischer Drüsen"—and the ideas it connotes are not likely to prove acceptable at present, for although it is clear that the underlying defect is an endogenous one, the evidence available does not support Naegeli's contention that the primary defect is in the ductless glands.

Since 1912, when Curschmann gave his classical description of dystrophia myotonica, much has been written upon the subject and the number of the recorded cases already approaches two hundred; nevertheless, the time has not yet arrived when descriptions of new cases are devoid of interest, for our information is still incomplete on many points, and a number of problems remain for the solution of which reports of

careful investigations on a large number of cases are still necessary. Further, very few cases have been examined after death, and our knowledge of the morbid anatomy of the disease is still meagre. We are able to give here an account of the findings in a case which was the first, so far as we are aware, to come to autopsy in this country; and descriptions are given of the morbid appearances in portions of muscle removed from two patients during life. In our general description of the disease we base our remarks upon twenty cases that have come under our own observation, and at the same time we draw freely upon a large number of papers that have appeared in foreign journals since this disease last formed the subject of a communication to English readers.

II.—Description of Cases.

Case 1.—William A., an army pensioner, aged 44 years, was admitted to the National Hospital under the care of one of us in February, 1922, complaining of "weakness in the arms and legs" of five years duration. He enjoyed good health until March, 1917, when, whilst undergoing military training, he underwent a severe feverish illness diagnosed as influenza. During convalescence from this illness he suffered from severe pains in the joints, especially in the knees, elbows and shoulders; the pains disappeared in a few months but left behind them a weakness in the legs, which soon spread to the arms and increased gradually as time went on. Early in 1918 he noticed for the first time an occasional difficulty in relaxing his grasp; the more firmly he grasped an object the more difficult it was to relax his hold. This symptom still troubles him. He cannot say with certainty whether this difficulty preceded or followed the onset of weakness in the arms, but he thinks that weakness came first. During the last year he has noticed a feeling of stiffness in the legs on rising to his feet and slowness in "getting off the mark" when he begins to walk: after the initial stiffness has worn off he can walk at a slow pace for about a quarter of an hour; the legs then begin to ache and he is forced to rest. He is quite steady on his feet, but on several occasions the legs have given way suddenly without apparent cause and he has fallen "like a log" in such a way that he has struck the back of his head. His weight is two stone less than it was before his illness began; his arms and legs have wasted and his facial appearance has altered very much during the last few years; his voice is not so clear as it used to be; his hair has fallen out freely, especially in front of his head; he has had no sexual intercourse for several years and desire is absent; his hands are "naturally cold" and they often "go blue"; his eyes water freely, especially when he is in the open air. Apart from weakness of the limbs he feels perfectly well. His eyesight is very good; he has no difficulty in chewing his food or in swallowing; the amount of sputum is not increased and he hardly ever perspires.

He was always very healthy until his present trouble began; he played football in his youth and was an unusually good long distance walker. For ten years before joining the Army he did heavy manual work in a mineral-water factory.

His parents died when he was a child from causes unknown to him; he has three sisters, all older than himself and all healthy; his only brother died in childhood of pneumonia. He has three daughters and one son living; one son died in infancy of pneumonia.

So far as he knows no member of any branch of his family has suffered from any muscular trouble or from cataract. One of his sisters and his only son were examined by us and found to be healthy. The son is a professional long-distance walker of repute; on one occasion he walked from his home to visit his father in hospital and returning on foot covered a distance of over one hundred miles in twenty-three hours.

Condition on examination: Height, 5 ft. 6 in.; weight, 7 st. 4 lb. Skull of normal size and shape; ears small, well-formed; face lacks expression, deep temporal hollows, sunken cheeks, smooth forehead, drooping eyelids, rather thick, slightly pursed lips. Skin on forehead very greasy, giving it the appearance of being covered with sweat; conjunctivæ slightly injected, eyes watery; tongue small and deeply furrowed; palatal arch very high and narrow; many teeth missing, many stumps, no prognathism; hair black, thin on vertex, marked frontal baldness; thin dark eyebrows, strong dark beard, shaves daily. Thyroid gland neither visible nor palpable; chest hairless, axillary and pubic hair scanty; nipples deeply pigmented; pubic hair of normal male distribution; no hair on arms or legs. Penis well formed and of normal size, testicles small and very soft; hands cold and blue, nails brittle, with deep longitudinal ridges, no lunulæ visible; texture of the skin normal, very little subcutaneous fat. Heart apex in fifth space in nipple line, sounds feeble, no murmurs; pulse regular, vessels healthy, average rate 80 per minute; blood pressure (Riva Rocci), systolic 105, diastolic 70 mm. Hg; lungs healthy.

Electrocardiogram (Dr. E. D. Adrian): "It has been stated that there is sometimes a lengthening of the A-V interval in patients with this disease. We therefore recorded the electrocardiogram leading from the right hand to the left foot. The A-V interval, or rather the P-R interval (between the summits of the P and R waves) was 0·16-0·17 second over a large number of cycles. This is well within the limits of the normal."

Barium meal (Dr. Russell Reynolds). Form and motility of stomach normal; no delay in passage through intestinal canal.

Urine: Specific gravity 1,015; contained no albumin or sugar. Blood count: Red blood cells 4,700,000, hæmoglobin 92 per cent; white blood cells 7,000, polymorphonuclear cells 65 per cent., lymphocytes 33 per cent., eosinophils 2 per cent.

Nervous and muscular systems.—The patient is even-tempered and sociable and submits with good grace to prolonged examinations; memory very good, takes an intelligent interest in his disease and is well-informed. His

expressionless face gives an impression of dulness and mental apathy which further acquaintance with him soon belies. Speech low-toned, monotonous and slightly muffled. Vision $\frac{6}{6}$ in both eyes; "no cataract, fundus normal" (Mr. Leslie Paton). Hearing, smell and taste normal. Pupils of moderate size, equal, and regular in outline, react well to light and on convergence; range of ocular movements complete, no nystagmus; corneal reflexes brisk and equal; temporal muscles wasted, masseters small but firm, and their power is slightly diminished. Typical myopathic facies with weakness of all the facial muscles, most marked in the orbiculares oculi; well-marked Chvostek's sign on both sides. Soft palate is not unduly thin, moves well on phonation, palatal reflex present, no dysphagia. All movements of the vocal cords appear to be normal on inspiration and phonation, although the appearance of the right cord leads one to infer that it is less tense than the left. The condition, however, is not sufficiently marked to be acceptable as evidence of definite paresis. The tongue is small and deeply wrinkled, and can be protruded with difficulty about half an inch beyond the teeth; on striking its lateral border with a small percussion hammer a deep dimple forms and persists for several seconds.

The neck is thin, the box of the larynx is unduly prominent, all the muscles of the neck are weak and wasted; deep hollows replace the normal prominence of the sternomastoids which are represented by a few fibrous strands; in the erect position the head is held bent forward; when he is lying down the head cannot be raised from the pillow, and when the trunk is raised the head falls back; the upper parts of both trapezii are slightly wasted, but the shoulders can be shrugged powerfully. There is no atrophy of any of the muscles of the shoulder-girdle, and the range of voluntary movement at the shoulder-joint is complete, though there is definite slight loss of power in all movements; no wasting in the upper arms, range of movement at the elbow complete, power of flexion very good, extension not quite so good; obvious wasting of all the muscles of the forearms, greatest in the extensors, especially in the supinator longus; extension at the wrist very feeble, flexion weak but better than extension; hand-grasps feeble; dynamometer R.30, L.28 (observer R.120, L.118); slight wasting of the muscles of the thenar and hypothenar eminences and power diminished out of proportion to the wasting; cannot touch tip of little finger with tip of thumb; writes rapidly with a pen in a good hand. No wasting of trunk muscles, but he is unable to rise from the supine to the sitting position without using his arms; repeated flexion and extension of the spine in the standing position is carried out slowly and soon tires; the muscles of the buttock are small and soft but not obviously wasted; power of all movements at the hip-joints is greatly diminished; when lying on his back the extended lower limb can be raised about 45°, but the attitude cannot be maintained for more than a few seconds. Flexion and extension at the knee-joint are weak, flexion being better than extension. The muscles on the antero-lateral aspect of the leg are definitely wasted; the calves are soft but bulky in comparison with the other muscles of the lower limbs; dorsiflexion of the feet is very weak, plantar flexion less so; throughout the lower limbs the loss of power is much

greater than the amount of wasting would suggest. The muscles generally are small and soft, the limbs are limp and offer little resistance to passive handling; all voluntary movements are well co-ordinated when he carries them out at his own slow pace, but alternating movements, especially when he attempts to perform them rapidly, are badly done; in attempting rapid alternating flexion and extension at the elbow for example, after the action has been repeated once or twice extension is begun before flexion is complete and vice versa, and later he begins to make adventitious movements at the wrist and shoulder-joints, so that after a time the arms are flung about in a most disorderly manner, the desired movement of flexion and extension being almost absent. The same defects of voluntary movement are present in the lower limbs; their explanation will be discussed later in the chapter on myotonia. All the tendon reflexes are absent.

The patient stands on a wide base with the head bent forward; there is a marked upper dorsal kyphosis and compensatory lumbar lordosis; he walks slowly with a slight "steppage" gait; in attempting to rise from the floor he proceeds in exactly the same manner as a patient with pseudo-hypertrophic paralysis up to the point of assuming the all-fours position, but he is unable to climb up his legs and is quite unable to gain the erect position; he cannot rise from a chair without using his arms. Fibrillation was observed in the thigh muscles on several occasions.

Myotonic symptoms: Myotonia on voluntary movement is extreme in the hand-grasps; on grasping the observer's hand firmly an associated movement of flexion occurs at the wrist; when the order is given to relax, the grip loosens at once and the fingers are extended just enough to allow the hand to be withdrawn; the fingers remain flexed at the metacarpophalangeal joint for many seconds, and flexion of the wrist persists for thirty seconds or even more; the difficulty in extending the fingers and wrist is greater the more power he exerts; it diminishes and then disappears with repetition of the movement. A similar delay in relaxation was demonstrable in the biceps and deltoid of both sides and in the extensors of the knees.

On stimulating the muscles mechanically by a firm blow with a percussion hammer a prolonged contraction, lasting sometimes as long as thirty seconds, was obtained in the tongue, the deltoids, the thenar and hypothenar eminences, the vastus externus and the calves. In the tongue the phenomenon is shown by the formation of a deep dimple on the lateral border at the point of impact; in the deltoids, where the prolonged contractions are most persistent and most easily elicited, a deep hollow forms at and around the point of impact: it is broadest at this point and is continued up and down in the length of the fibres as a distinct furrow; this is seen in the vasti and calves as well. In the thenar eminence the muscles stand up prominently and the thumb is strongly adducted; in the hypothenar eminence the muscle stands out, the little finger is abducted and remains in this position for ten seconds or more. It is noticed that in the muscles showing much atrophy the normal myotatic irritability is absent, and that the myotonic after-contraction is most easily demonstrated in

the muscles that have retained their bulk. In the pectoral muscles, however, sharp percussion produces a typical "harp-string contraction" of normal duration, whilst at the point of impact a little elevation forms and persists for a few seconds, just as it does in many healthy individuals.

Electrical reactions.—To direct faradism the excitability of the following muscles was greatly diminished: Flexors and extensors of the forearm, extensors of the knee and dorsiflexors of the foot. No response was obtained from the sternomastoids or from the tibialis anticus. Normal twitches were obtained from all the other accessible muscles: in the deltoids, the flexors of the forearm and the soleus of both sides, short stimuli evoked a normal twitch; with a stimulus of longer duration the contraction persisted as long as the current was passing and for several seconds after it was withdrawn.

To direct galvanism no reaction was obtained from the sterno-mastoids or tibialis anticus, and the excitability of the extensors of the forearms, extensors of the knees and the dorsiflexors of the feet was greatly reduced; in several muscles A.C.C. was definitely greater than K.C.C. From a number of muscles—e.g., deltoids, thenar and hypothenar eminences, extensors of knee, hamstrings, solei and peronei—normal twitches could not be obtained, but a tetanic contraction occurred and persisted as long as the current was passing; as a rule the muscle relaxed as soon as the stimulus ceased, but in the deltoids, small muscles of the hands and solei, there was a myotonic after-contraction; this phenomenon was evoked more readily from the anode than from the cathode.

Dr. E. D. Adrian kindly undertook the investigation of the electrical reactions of the muscles and has given us the following report:—

The response to electrical stimulation.—The curve relating the strength and duration of current required to excite [1] was determined for two muscles, the deltoid and the flexor carpi radialis of the right arm. Both these muscles gave well-marked myotonic phenomena, but the strength-duration curve shows nothing abnormal. This may be seen from fig. 1 which gives the curve for the flexor carpi radialis and, for comparison, a curve for the same muscle in a perfectly healthy subject. The chronaxie (the duration corresponding to a strength twice as great as the threshold value at infinite duration) is 0·0002 second for the flexor carpi radialis and 0·00015 second for the deltoid, the range of variation in healthy subjects being 0·00008 second to 0·0006 second. The absence of any marked change in the curve is not to be wondered at in view of the fact that currents of short duration probably take effect on the motor nerve fibres and not on the muscle substance itself.

With currents of long duration the response was abnormal. (1) For example, with the galvanic current when the key was opened and closed by hand the muscle remained contracted as long as the current was passing instead of contracting at make and break only. We are unable to say whether this persistent contraction was localized to the neighbourhood of the electrodes, but it did not cause any marked shortening of the muscle. (2) With very strong currents (over ten times the threshold value), even though the duration was shorter than 0·001 second, the muscle relaxed slowly. (3) With inter-

mediate durations (0·05 second), even with weak current strengths a double twitch of the muscle was often observed. (4) With weak currents of less than 0·001 second duration, such as single shocks from a faradic coil, the muscle twitch showed no departure from the normal. Myographic tracings of such muscle twitches gave a rapid rise and fall exactly like that of a normal muscle.

These results point to an abnormality in the muscle fibre rather than in the nerve, but they do not allow us to go any farther in suggesting the nature of the abnormality.

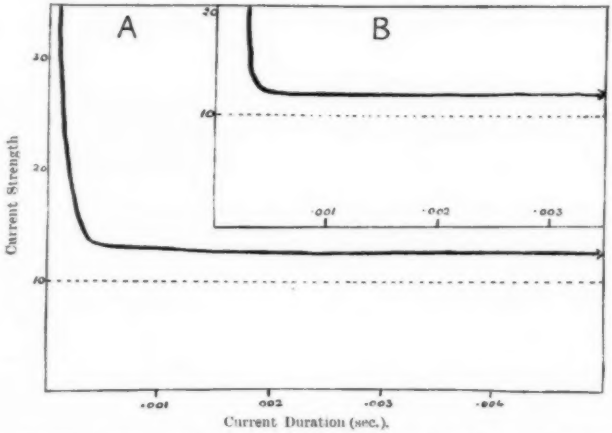

FIG. 1.—*Case* 1. "Chronaxie" curves for (A) flexor carpi radialis in Case 1, and (B) for normal muscle.

The electromyogram.—The action current in the deltoid during voluntary contraction was recorded with the string galvanometer. Non-polarizable electrodes (Zn, ZnCl, NaCl) were strapped to the shoulder and the patient was made to contract the muscle against resistance. A typical record is shown in fig. 2. This gives the irregular action currents at the beginning of the contraction (fig. 2, *a*), and the more regular oscillations occurring after the contraction had been maintained for two and a half seconds (fig. 2, *b*). A very irregular rhythm at the beginning of a contraction and a more regular one later on is not very uncommon in a normal muscle, though the regularity in this case seems to be greater than usual. The oscillations have the normal frequency of about fifty a second.

The most interesting part of these records occurred when the patient was told to stop contracting. The large oscillations cease in about half a second, and after this the string shows no more than the usual very small irregularities which are present when the muscle is at rest (fig. 2, *c*). The muscle does not

relax completely, however, until ten to fifteen seconds after the order to stop. Thus the persistent after-contraction is not accompanied by an oscillating electric response of the type found in the voluntary contraction; in fact it is not accompanied by any electric response that could be detected by the means at our disposal. (It should be mentioned that we were not working with a specially sensitive system.)

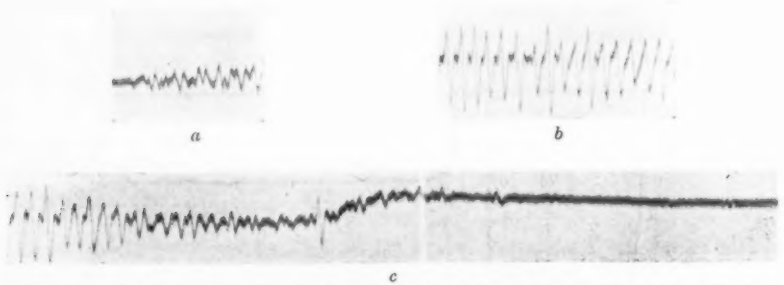

FIG. 2 (*a*, *b* and *c*).—*Case* 1. Tracings taken by string galvanometer of the voluntary contraction of the deltoid muscle in Case 1 (*a*) at the beginning of contraction; (*b*) during contraction; (*c*) during relaxation. At the beginning of the tracing (*c*) the patient was told to relax the muscle, which, however, remained in contraction for about ten seconds longer, although the nervous stimuli to it, as shown by the galvanometer tracing, ceased in less than one second. The waves of nervous impulse are at a rate of about fifty per second.

FIG. 3.—*Case* 1. String galvanometer tracing, showing the effect of direct percussion of the deltoid muscle. A single wave is shown by the galvanometer, although the contraction of the muscle persisted for several seconds.

The same holds good for the persistent local contraction produced by striking the muscle with a percussion hammer (fig. 3). The blow itself caused a rapid displacement of the string, which may have been due to a shifting of the electrodes or may have been a single action current, but the string returned to rest long before the local contraction had subsided.

The absence of electric response in the myotonic effect can be most simply explained on the following lines. There can be little doubt that the large electric oscillations are due to impulses of nervous origin sweeping through the muscle. These cease when the patient stops contracting voluntarily. The persistent after-effect in the myotonic muscle is therefore not maintained by impulses from the central nervous system, but is due to some abnormality in the muscle fibre. A persistent contraction of this type need not be associated with any form of electric response, for even in the single twitch of a normal muscle the action current is over some time before the muscle has relaxed.

These results bring us no nearer to deciding the exact mechanism of the persistent after-contraction, though they confirm the view that it is of muscular and not of nervous origin. It might be thought that they give some support to the doctrine that the "tonic contraction" differs from a tetanus in that it is not associated with an oscillating electric response. This doctrine has been the subject of much discussion recently [22], and we do not propose to deal with it except to point out that the persistent after-contraction in myotonic muscles need not have anything to do with the long-continued, postural contractions to which the name "tonic" is commonly applied. A discussion of the different factors which may be involved in a persistent contraction of muscular origin is given in a recent paper by Hartree and Hill [23] on "The Mechanism of the Veratrin Contraction."

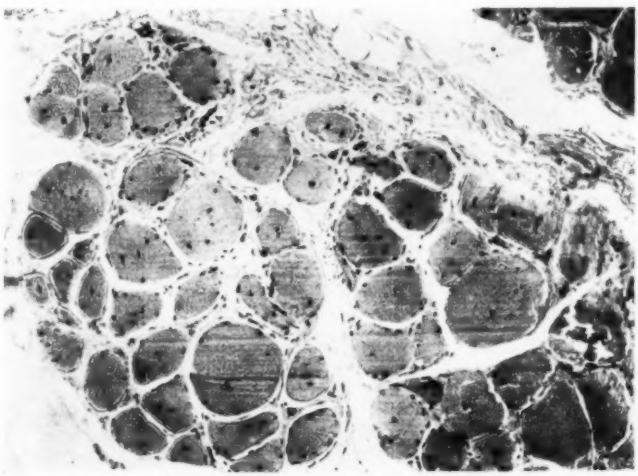

FIG. 4*a*.

Histological examination of a portion of excised muscle.—A piece of the right deltoid muscle removed by open operation was fixed in formalin saline and embedded in celloidin; sections of it were stained with alum hæmatoxylin and van Gieson's counterstain. These sections showed very striking alterations which are illustrated in fig. 4. The fibres were of very varying size, ranging from 8 μ to 150 μ in transverse diameter. On cross-section almost all were of rounded outline, and the connective tissue between the individual fibres appeared to be rather thicker than normal. On longitudinal section some of the fibres showed localized swellings, which were associated with some loss of the transverse striation, and in most of the fibres the longitudinal striation was exaggerated. The sarcolemma nuclei were much more numerous

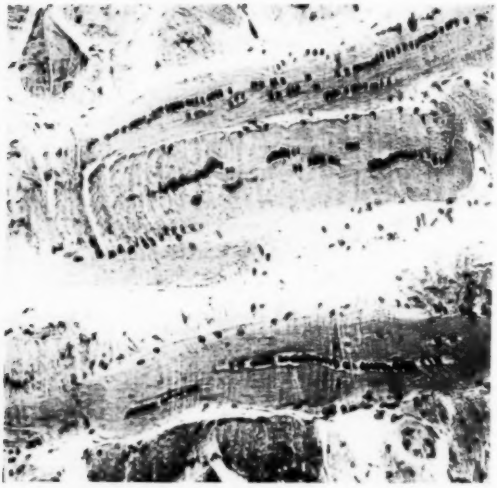

FIG. 4*b*.

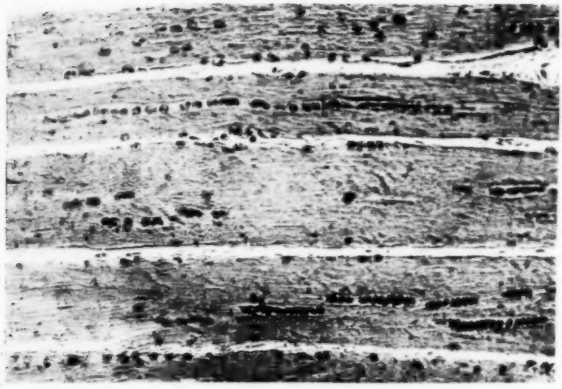

FIG. 4*c*.

FIG. 4 (*a*, *b* and *c*).—*Case* 1. (*a*) Transverse, and (*b* and *c*) longitudinal sections of deltoid muscle. Note in (*a*) internal nuclei and excess of connective tissue between the rounded fibres. In *b* and *c* several chains of internal nuclei are seen, some of which are surrounded by a clear zone.

than normal, and in many places dark-staining nuclear masses lay between the muscle fibres. Many nuclei were also seen within the muscle fibres—in fact, almost every fibre contained some nuclei in its substance. These nuclei were often arranged in chains running down the centre of the fibre.

Three stages of this change appeared to exist: (1) In the first stage the nuclei are elongated and lie end to end, separated from one another by a definite interval, which is, however, much shorter than the length of the nucleus. (2) In the second stage the nuclei are oval or rounded, and lie much closer to one another, so that, although they remain separate, there is no definite interval between them. (3) The third stage consists of the apparent or absolute fusion of the nuclei to form beaded rods, sometimes of considerable length. When the outline of the individual nuclei can be traced, they are seen to be wider than they are long, and either oval or flattened at the opposed surfaces like rouleaux of red-blood corpuscles. In a few instances two such nuclear rods could be seen lying side by side, but in most cases they were single. One or two muscle fibres consisted almost entirely of such a beaded nuclear rod, to which the sarcoplasm formed a very thin covering.

This case conforms to the classical descriptions of dystrophia myotonica given by Batten, Steinert and Curschmann, in almost every respect. With a well-marked facies myopathica and a characteristic alteration of speech there is muscular atrophy of peculiar distribution, greatest in the sternomastoids, the muscles of the forearms and the muscles on the antero-lateral aspect of the legs; active myotonia is most prominent in the hand-grasps, mechanical myotonia is of wider distribution, and a typical myotonic after-contraction on electrical stimulation is present in a few muscles only. There are numerous general dystrophic phenomena, including baldness, atrophy of the testicles with loss of sexual power, loss of body weight, acrocyanosis and increased secretion of tears; all the tendon reflexes in the upper limbs and the knee-jerks are abolished.

Case 2.—John R., aged 31, was admitted to the National Hospital, Queen Square, under the care of one of us, in August 1922, complaining of "difficulty in letting things go" and "stiffness in the legs" of seven years duration. Apart from an attack of influenza in 1917, he was always healthy; prior to the outbreak of the Great War he worked as a hairdresser and played football as a professional. Soon after joining the Army in 1914 he underwent an examination in rifle drill for promotion: during this examination, when he was bent on carrying out the various movements smartly, he suddenly found himself unable to withdraw his hand from his rifle which he had just brought to the slope-arms position, and since then this difficulty in relaxing a firm grasp has persisted. He was not promoted, but his defect did not prevent him from completing his military training and proceeding to Gallipoli, where he was

wounded at the landing. After his discharge he returned to his former occupation, but he found that his work was slow and that his earning capacity was greatly diminished; he could work with the scissors fairly well, but the hair-clipping machine caused difficulty because the grip had to be firm. He continued to play football once a week for an amateur team; his game was not so good as it used to be, but he could still "give most of them points," and the old professional enjoyed his game with the amateurs because he was able "to run rings round them." Occasionally when he began to run his feet "buckled up," "the toes turned down and the foot became hollow," "it was a sort of spasm." The spasm was not painful, but he was obliged to stand still for a minute or so until it relaxed. Like the difficulty in the hand, which diminishes with repetition of the movement which caused it, this spasm in the feet was only troublesome at the beginning of a game. He has noticed that if he sits in a squatting position for a few minutes he is unable to rise again without assistance because of "a stiffness in the knees."

His speech is not so clear as it used to be: sometimes when he bites anything hard the muscles of the jaw go stiff, and he often notices a stiffness in the jaws when he chews his food, so that he is forced to masticate slowly; sometimes, too, food sticks in the back of his throat and refuses to go down. He has lost more than a stone in weight during the last year, his hands are always blue and cold. Apart from the troubles already mentioned he has nothing to complain of and feels perfectly well. His father died of diabetes at the age of 61, his mother is still alive and well; one brother, two step-brothers and three sisters are all healthy; all of them have married and two of them have several healthy children. He has a healthy son aged 4. He knows nothing of his other relations

On examination: Height 5 ft. 7 in., weight 9 st. Skull of normal size and form; face very narrow, prominent cheek bones, deep temporal hollows, hollow cheeks, slightly drooping lids, rather thick slightly pursed lips; forehead greasy; large well-formed prominent ears; conjunctivæ not injected, no watering of the eyes; tongue small and deeply wrinkled; palatal arch very high and very narrow; many teeth missing, remainder decayed; no prognathism; hair on head black, marked frontal baldness, thick dark eyebrows, dark beard, shaves daily; thyroid very small; a few dark hairs on the chest, axillary and pubic hair normal in amount and distribution, arms and legs almost hairless; nipples deeply pigmented, skin on neck and upper part of trunk shows uniform brownish pigmentation; testicles very small, especially the left, and very soft, penis large; hands cold and blue, finger nails ridged longitudinally, lunula visible in right thumb-nail only; texture of skin normal, moderate amount of subcutaneous fat.

Heart apex beat in fifth space, ½ in. internal to the nipple line; sounds feeble, pulse regular, 72 per minute, arteries healthy. Urine: specific gravity 1015, contains no albumin or sugar. Lungs healthy. Has great difficulty in getting the bowels to act, abdominal viscera otherwise healthy. Wassermann reaction in blood and cerebrospinal fluid negative. The latter was clear and

colourless, contained 3 cells per c.mm., and total protein 0·025 per cent. Nonne-Apelt test negative. Lange 0001110110.

Nervous and muscular systems: Patient is intelligent and well-informed, takes an active interest in passing events and discusses them freely with his comrades; he is rather reticent about his illness and is inclined to resent examination, but it cannot be said that he shows any marked temperamental or psychical defects. Speech is low toned, monotonous and slightly muffled. Vision $\frac{6}{6}$ in both eyes, media and fundus normal, no cataract. Hearing, smell and taste normal. Pupils of moderate size, react well to light and on convergence; range of ocular movements complete, no nystagmus; corneal reflexes brisk and equal; temporal muscles wasted, masseters small and soft, forehead free from wrinkles; slight ptosis of both lids, complete lack of emotional movement of face in conversation, distinct weakness of all the facial muscles in voluntary movement, greatest in the orbiculares oculi; no Chvostek's sign; soft palate thin, does not move well on phonation, palatal reflex present; the tongue is small and deeply wrinkled but its movements are normal; on percussing the edge of the tongue a deep dimple forms and persists for several seconds. The sternomastoids are weak and much wasted; there is no appreciable weakness or wasting of any other muscle. The muscles are moderately firm to the touch and the limbs offer a normal amount of resistance to passive movements. There is no inco-ordination of movement and rapid alternating movements are well performed.

The tendon reflexes in the arms and legs are absent; abdominal reflexes brisk and equal on the two sides; plantar reflexes flexor. No subjective or objective sensory disturbances: sphincters normal. Gait normal, no rombergism.

Myotonia.—Active myotonia is demonstrable in the hand grasps only, the difficulty in opening the hand is greatest at the first effort and diminishes rapidly with repetition; mechanical myotonia: on striking the muscles with a percussion hammer, typical myotonic contractions were obtained in the tongue and in all the accessible muscles of the upper and lower limbs; it was not found in any of the trunk muscles.

Electrical reactions.—To direct and indirect faradism the reactions were normal except for a diminution in the sternomastoids to direct stimulation. To direct galvanic stimulation the response in all the accessible limb muscles was abnormal in that contractions did not occur at make and break only but persisted as long as the current was passing; in the flexors of the forearms the contraction persisted after the stimulus was withdrawn, but in all the other muscles relaxation occurred with cessation of the stimulus.

In this case the diagnosis is founded on the association of muscular atrophy of peculiar distribution—facies myopathica and atrophy of the sternomastoids—with active myotonia most conspicuous in the hand-grasps, reactive myotonia of wider distribution, and a number of general symptoms including atrophy of the testicles, baldness, and acrocyanosis.

Case 3.—Edith B., aged 41, a children's nurse, was admitted to the National Hospital, Queen Square, under the care of Dr. Risien Russell, in November, 1922, for "sudden falls and weakness" of four years' duration. She enjoyed perfect health until four years ago, when she began to "fall to the ground helpless two or three times every day." The attacks, which were regarded as "a kind of fit," came on without warning and without apparent cause; consciousness was unaffected, but the whole body became rigid, and she was quite helpless for a minute or two; she then rose to her feet again, feeling none the worse for the attack. At that time she was "able to walk miles," and she had not detected any weakness in the limbs. This went on for three months; she then went to a doctor, on whose advice she had all her teeth removed; after this the falls became much less frequent.

About a year ago she began to tire easily in walking, and had difficulty in climbing stairs. About the same time she noticed that if she grasped an object firmly, the hand "shut up tightly, and would not open again." Sometimes the right hand closed up of its own accord and remained closed for a minute or more.

Apart from general weakness and the spasms in the hands, she feels perfectly well. She has lost a lot of weight during the last few years; the arms and legs are much thinner than they used to be, and her facial appearance has altered; her hair is falling out freely, her voice is not so clear as it used to be; she has never had a friend of the male sex, and the thought of marriage has never appealed to her; the menstrual periods are still regular; she sees well with glasses; she has never noticed any increase in the amount of sputum, sweat, or tears; the hands are always blue and cold.

She had been very healthy until the present trouble began. Her father died of tuberculosis at the age of 58, her mother of cancer at the age of 76; she has four brothers—two are healthy, but two, one older and one younger than herself, suffer from the same disease as herself. They have the same "woe-begone" expression—one of them cannot close his eyes, and both of them are getting gradually weaker. So far as she knows, they have never had any difficulty in letting things go. She has never heard of any muscular or nervous trouble in any other member of the family, or of cataract.

Condition on examination.—Height 5 ft. 3 in.; weight 6 st.; skull of normal size and shape; ears small, well-formed; face lacks expression, deep temporal hollows, sunken cheeks, smooth forehead, drooping lids, slightly pursed lips, edentulous, very high, narrow, hard palate; hair on head scanty, light brown, becoming grey; axillary and pubic hair normal in amount and distribution, other parts hairless; thyroid gland enlarged and firm, breasts normal; hands cold and blue; nails brittle—"I try to get them long, but they always break off"—no lunulæ; skin healthy, very little subcutaneous fat. Abdominal and thoracic viscera healthy. Blood count: Red blood cells, 5,600,000; hæmoglobin, 100 per cent.; white blood cells, 6,650; polymorphonuclear cells, 59·5 per cent.; lymphocytes, 34·5 per cent.; hyaline, 5·5 per cent.; eosinophils, 0·5 per cent.

The patient is intelligent, has a very good memory, makes an excellent witness, and is a pleasant person, entirely free from the temperamental defects which are so common in this disease. Speech is low-toned, monotonous, and muffled. Hearing, smell, and taste are normal. Vision $\frac{6}{9}$, with glasses right and left.

"In the right eye the periphery of the lens shows a complete ring of dust-like opacities lying mostly anterior, with one or two streaks radiating from the periphery and lying posterior to the ring of opacities. In the left lens the same dust-like opacities and the same radiating streaks are seen." (Mr. Leslie Paton.)

Pupils of moderate size, equal, regular in outline, react well to light and on convergence; range of ocular movements complete, no nystagmus, diplopia, or strabismus. Corneal reflexes present; extreme wasting of the temporal muscles, masseters small, but firm, no difficulty in chewing. Typical myopathic face, with weakness of all the facial muscles, especially the orbiculares oculi; no Chvostek's sign. Soft palate not unduly thin, palatal reflex present, no difficulty in swallowing. Tongue small, movements of good range and power, well-marked myotonic after-contraction on percussion.

The sternomastoids show extreme atrophy, and all the movements of the neck are very weak; when she is lying down, the head cannot be raised from the pillow, and if the trunk is raised passively the head falls back; the muscles of the trunk and of the shoulder and pelvic girdles are small, but not obviously wasted, and their power is retained; atrophy is severe in the forearms and in the small muscles of the hands, and all these muscles are very weak, especially the extensors of the wrists and fingers; in the lower limbs there is severe atrophy of all the muscles below the knee and of the vasti of the thighs; the power of dorsiflexion of the foot is almost lost.

All the tendon reflexes in the upper and lower limbs are present, but they are very feeble; the abdominal reflexes are brisk; the plantar response is normal. No objective sensory disturbance was detected.

Active myotonia is confined to the hand-grasps, mechanical myotonia is present in the tongue, deltoids, and thighs.

The patient walks slowly on a wide base with the eyes directed to the ground and with a definite "steppage" gait.

There is no sphincter disturbance.

Histological examination of a portion of excised muscle.—Pieces of the right deltoid muscle removed by open operation were fixed in 5 per cent. trichloracetic acid, and in 10 per cent. formalin saline solution. The former fixative was employed as being that which Heidenhain used to demonstrate the appearance of coils of muscle fibril round the muscle fibres (*v. infra*). We were, however, unable after prolonged searching to see anything resembling this phenomenon. This fixative seemed to produce considerable swelling of the muscle fibres, and we therefore base our description of the histological appearances of this muscle on sections of the piece fixed in formalin saline. These revealed comparatively slight alterations from the normal. The muscle fibres appeared to be unduly rounded, and the sarcolemma nuclei were definitely

increased in number. Many of the fibres contained central nuclei and these were often arranged in chains corresponding to the first stage described in Case 1. But in many fibres no central nuclei could be seen. A few of the fibres were shrunken, stained a browner colour than usual with van Gieson's counterstain, and contained a large number of nuclei within them. The majority of the fibres were of normal thickness, and in none could we demonstrate any loss of the transverse or increase of the longitudinal striation.

Case 4.—The patient came under observation at the National Hospital in 1906 when he was 24 years of age, and was described by Batten and Gibb (Case 5) in their original paper on myotonia atrophica. He died at the age of 39 years in the Infirmary of St. Mary's, Islington, in 1921, and through the kindness of the Superintendant, Dr. Arthur Robinson, one of us was able to perform a post-mortem examination thirty-six hours after death.

Post-mortem examination.—The body was extremely thin and emaciated. There was a rounded kyphosis in the upper thoracic region. The limbs were greatly atrophied, especially below the knees and elbows.

The brain and spinal cord were removed and showed no abnormality to the naked eye. The thyroid gland appeared to be normal. The right lung was adherent to the pleura all over, especially at its apex, and was densely infiltrated all through with recent peri-bronchial tuberculosis. At its apex there was a small tubercular cavity the size of a walnut. The right lung showed some old and recent tuberculosis at its apex but not elsewhere.

The heart was healthy and there was very little atheroma of the aorta. The liver was normal ; the spleen was enlarged and congested but presented no sign of tuberculosis. The kidneys were healthy. The suprarenal glands were of normal size, their cortex in places was of a greyish colour, contrasting with other areas which showed the normal light brick colour ; the medulla was normal. The stomach and intestines showed no abnormality.

Muscles : The sternomastoids of both sides were represented only by a very thin band of fibres just under the skin, which was much smaller than the omo-hyoid muscle. The muscles of the forearms, and especially the small muscles of the hands and the anterior tibial and peroneal groups, were very pale and atrophied. Some of the bundles of the erector spinæ group were also very pale, whereas others presented the normal colour and consistence. The abdominal muscles and the hamstrings were well developed and dark in colour.

Pieces of various organs, muscles and nerves were preserved in 10 per cent. formalin saline solution for further examination.

Microscopic examination.—Sections of the right lung showed the appearances of early tubercular broncho-pneumonia, with only the earliest stages of caseation and very few tubercular giant cells. No tubercle bacilli were found in the sections.

The pituitary gland contained a great excess of colloid in the pars

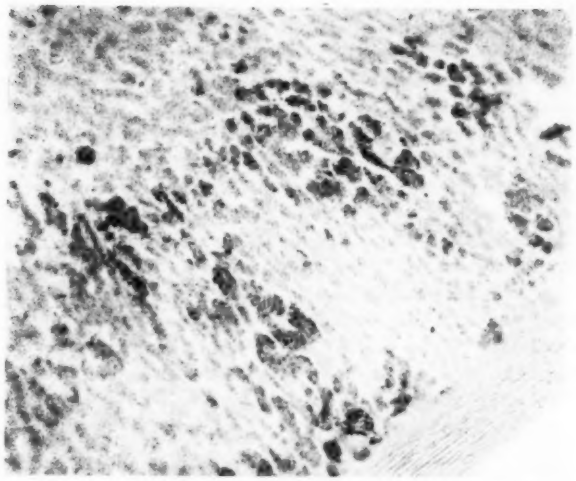

FIG. 5.—*Case* 4. Cortex of suprarenal in Case 4 stained by Scharlach R. and hæmatoxylin, showing the very irregular distribution of the cortical lipoid.

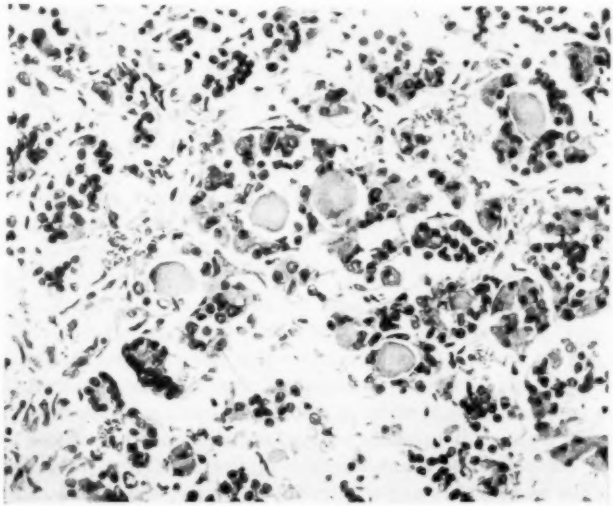

FIG. 6.—*Case* 4. Pars anterior hypophysis in Case 4, showing numerous particles of colloid in the gland acini.

intermedia, and fairly numerous small acini filled with colloid in the pars anterior.

The suprarenal glands showed a very patchy distribution of the cortical lipoid. In places there was none at all, whereas in others it was abundant. The medullary substance appeared to be normal.

Central nervous system.—Sections of brain-stem and spinal cord stained by the Kultschitsky-Pal method for myelin sheaths showed no degeneration either of fibre tracts or of nerve roots. There was certainly no trace of degeneration of the dorsal columns of the cord. Sections stained by toluidin blue showed that the Nissl granules were everywhere well preserved. The motor cells of the cord in the cervical and lumbar enlargements, as elsewhere, were of the normal polygonal shape and their Nissl granules large and angular. They contained no excess of lipochrome.

By hæmatoxylin van Gieson staining there appeared to be slight thickening of the pia-arachnoid in the cervical region, and there was also an excess of small round cells in the dorsal and ventral roots and in the perivascular channels of the larger veins at this level. This change may be probably accounted for by the pleurisy and tubercular broncho-pneumonia from which the patient died.

The sciatic, median and musculospiral nerves stained by the Weigert-Pal (Kultschitzky-Pal) method and by hæmotoxylin with van Gieson's counterstain were found to be healthy.

Muscles: Pieces of muscle from various parts of the body were embedded in celloidin after fixation in 10 per cent. formalin saline solution, and the sections stained by alum hæmatoxylin and van Gieson's counterstain. Some of the muscles showed great change, others little departure from the normal. The latter will be described first.

The biceps flexor cruris and triceps were practically normal. In them the nuclei were confined to the sarcolemma sheath and were not unduly numerous. The fibres on cross section were polygonal in shape and on longitudinal section showed the cross striation perfectly. Some pieces of the erector spinæ group examined were comparatively healthy. In other pieces some of the fibres were thinner and the nuclei more numerous than normal, while others had swollen to about four-thirds of their normal size and showed an excessive number of sarcolemma nuclei both in the sheath and within the substance of the fibres; these nuclei did not form chains within the fibre such as were seen in more affected muscles. In these large fibres the transverse striation was less apparent and the longitudinal striation more apparent than normal.

Some parts of the sartorius were normal, with the exception that they contained here and there groups of fibres of rounded outline which were furnished with an undue number of sarcolemma nuclei; other parts consisted of only a few rounded muscle fibres lying together in the middle of fatty tissue. In these fibres the sarcolemma nuclei, although excessive, were almost all confined to the surface.

The sternomastoid showed an analogous condition. Those parts of the

muscle which remained appeared practically normal. In other parts no muscle fibres were present, their place being taken by connective tissue and fat, but it was clear from the number of nerves and small arteries, and from the occasional presence of a muscle spindle, that the tissue had originally been muscle. Between the healthy muscle and the areas from which it had disappeared there was a zone in which the muscle fibres became more and more sparse, until only single rounded fibres were found in an area of connective tissue and nerve fibres. This gradual transition made it clear that the healthy muscle was really the sternomastoid and not, as at first appeared possible, a piece of overlying platysma which had been included with the sternomastoid.

The peroneal group showed no gross atrophy of the muscle, but there were definite changes in the muscle fibres. Most of them were fairly large and some were swollen up to 100 μ and 120 μ, which was the largest fibre measured in any muscle in this case. In these large fibres the cross striation

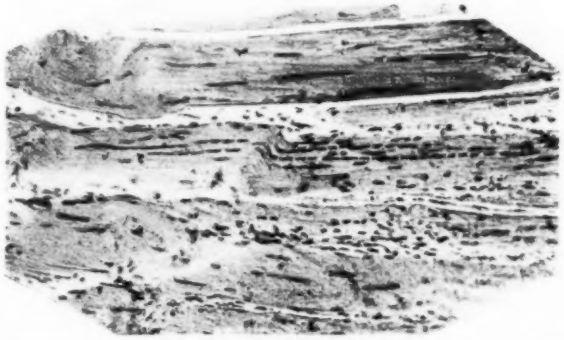

FIG. 7.—*Case* 4. Longitudinal section of peroneal muscle in Case 4, showing chains of internal nuclei.

was usually poorly marked but still apparent, and on cross section many of them showed clear or relatively pale central areas. Some such fibres had broken up into leashes of thin fibres.

Many of the muscle fibres in this group of muscles contained chains of nuclei similar to those described in the deltoid muscle in Case 1. The majority of these chains corresponded to the first stage as there described, a smaller number approximating to stage (2).

The tibialis anticus and long extensors of the toes were almost completely atrophied. In only one or two places were there small groups of medium-sized rounded muscle fibres lying singly in the connective tissue. Most of these fibres showed a few central sarcolemma nuclei, but none on the outside of the fibre. It was only possible to trace the origin of the rest of the tissue from muscle by the excessive number of small nerves and blood-vessels which it contained, and by the occasional presence of a muscle spindle near these. The

latter, although preserved more than the muscle fibres, were for the most part atrophied to some extent, showing only one or two fine muscle fibres in an overgrown ring of connective tissue. One perfectly normal muscle spindle was found, however, in an area from which all the muscle fibres had disappeared. This group of muscles undoubtedly showed the greatest degree of atrophy of any examined in this case.

In the flexor sublimis digitorum most of the muscle fibres were preserved, but showed great variation in thickness. The largest seen measured 75μ, and numerous thin fibres which appeared to arise by longitudinal fissuring of the larger fibres were present. The sarcolemma nuclei were in great excess, and

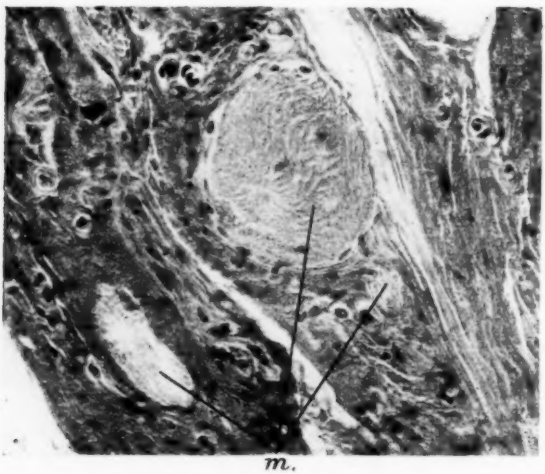

FIG. 8.—*Case* 4. Transverse section of tibialis anticus muscle in Case 4, showing a few muscle fibres (*m*) persisting in the midst of dense fibrous tissue.

central chains of nuclei similar to those seen in the peroneal group were very abundant and striking. In some places the nuclei of the sheath were proliferated to form dense purple masses between the muscle fibres (fig. 9, *b*). In a few of the muscle fibres the cross striation was less apparent than normal, but this change had no relation to the number of nuclei either in or within the sheath.

The small muscles of the thumb normally contain a considerable amount of fibrous tissue between the muscle fibres, but in this case the fibrosis appeared to be excessive, so that most of the fibres were rounded and isolated from one another by fibrous tissue. Some of the fibres showed longitudinal fissuring, and in a certain number central chains of nuclei were seen, but these were not so numerous or so long as those in the peronei and the long flexors of the fingers. The largest muscle fibres seen in this group measured 75 μ, the

smaller ones measured 20 μ or less. In places the muscle fibres appeared to be replaced by fibrous tissue. A few muscle spindles were present in these areas of atrophy, but they were very scarce and difficult to find.

FIG. 9*a*.

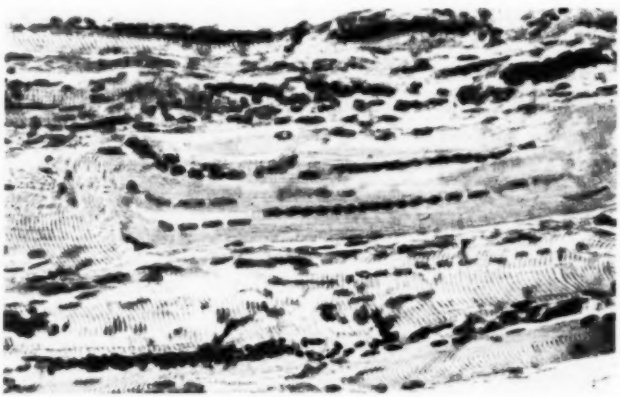

FIG. 9*b*.

FIG. 9 (*a* and *b*).—*Case* 4. Sections of flexor sublimis digitorum muscle in Case 4. In (*a*) a large fibre with large internal nuclei is seen in transverse section. In (*b*) similar internal nuclei are seen in longitudinal section, and there are dense collections of nuclei between the muscle fibres.

III.—GENERAL DESCRIPTION OF THE DISEASE.

Onset and Course.

The age of onset is usually between 20 and 35 years; occasionally it occurs in the late 'teens and in rare instances even earlier; Hauptmann [25] and Grund [20] have each described a case in which symptoms appeared at the age of 10 years.

In a surprisingly large number of reports the statement is made that the patient had been unusually proficient in athletics or gymnastics. One of our patients was a long-distance walker, another a professional footballer; this seems to prove that in some of the cases at least the muscles are perfectly healthy during youth and early manhood. The mode of onset varies greatly; in many instances it is insidious, coming on without any apparent exciting cause and the patient is unable to set a date to the first appearance of his trouble; in others, especially when some form of myotonic disturbance has been the first symptom, the onset is sudden and dramatic and its exact date is known. In a number of cases some feverish illness has served to disclose a weakness of the muscles that had not been noticed before; in our first case and in cases described by Batten, Rossolimo, Hoffmann, Curschmann, Rohrer, Rülf and others, severe pains in the limbs have been a conspicuous feature in the early stages; the nature of these pains is obscure but they are certainly frequent, and although they have not received special mention by previous writers it seems to us that they might well be included amongst the characteristic features of the disease.

According to Rohrer's statistics the first subjective symptom has been myotonia or weakness in about an equal number of cases, but this does not decide the old question of priority of symptoms, for objective examination often discloses the presence of one or the other, although it has given rise to no subjective disturbance. In our patient, J.R., myotonic symptoms have been present for seven years and although there is atrophy of the face and neck muscles the limbs are strong and he makes no complaint of weakness; other cases have been described in which myotonia has preceded weakness by an even longer interval. Moreover, undoubted cases of dystrophia myotonica have been described in which myotonia was a prominent symptom whilst weakness and atrophy were entirely absent; in some cases then myotonia certainly appears first. Those who oppose the contention that it always appears first, and practically every modern writer on the subject is included in this category, base their opinion on the findings in a few advanced cases in which myotonic signs could not be demonstrated at the time of examination of patients who gave no history of myotonic symptoms; but many patients in whom myotonia can be demonstrated objectively have never had subjective symptoms; objective myotonia is notoriously variable, and it tends to disappear in the late stages when atrophy is severe; absence of

myotonia therefore has not the same evidential value as absence of atrophy, hence we conclude that myotonia certainly appears first in some cases and probably in all, whereas there is no proof at present that it may be preceded by muscular atrophy. Further reference to the site and mode of onset of muscular atrophy and myotonia will be made in the following chapter.

The course of the disease is usually extremely slow; our patient, W. A., however, was severely incapacitated within a year of the onset, and the same rapid course was observed by Hauptmann in a man who had served in the trenches for a long period during the Great War; within a year of the onset weakness and atrophy were widespread and severe. Life is rarely prolonged after the 45th year; the oldest patient in the records is one of Oppenheim's who lived to the age of 50. Tuberculosis has been named as the commonest cause of death; it was the cause in our patient F. W., but Fleischer denies that it is common; in many cases death seems to have been the result not of intercurrent disease, but of that curious "asthenia" which so often supervenes in chronic disease of the muscular and nervous systems.

(2) *Muscular Atrophy and Myotonia.*

An examination of a large number of patients suffering from dystrophia myotonica, with special reference to the extent and intensity of muscular atrophy and myotonia, reveals the fact that these show considerable variations. At one end of the series there are cases in which atrophy is widespread and severe and many muscles are myotonic; in an intermediate position there are many in which one is severe whilst the other is slight, or both are present in a minor degree, and every gradation is encountered until we come to the rare cases in which one or the other is absent. Hence, although a bare knowledge of the facts that muscular atrophy is usually found in the face, neck and forearms, and that myotonia is usually present in the hand-grasps, will enable the observer to recognize typical cases, a much more profound knowledge is necessary if the numerous cases that diverge widely from the classical Batten-Curschmann type are not to escape detection. It might be thought that the severity of the symptoms would depend on the duration of the disease, but this is by no means the case.

Myotonia.—From its former position as the primary and essential symptom of the disease myotonia has been relegated by general consent to a rank equivalent with the other cardinal symptoms; and certain authors (Curschmann, Rohrer, Naegeli) have attempted to place it in

an entirely subordinate position. Nevertheless, we place it first because it is certainly the most constant symptom, and because, in our opinion, it still holds its place as a most important feature of the disease. The slow relaxation of muscular contractions that constitutes the symptom may occur after active movements, or after contractions elicited by mechanical or electrical stimulations; as a rule it is present in more than one form, some muscles perhaps showing it to one kind of stimulation, some to another, but it may be present in any one form alone. All writers agree that active myotonia is shown most frequently by difficulty in relaxing the hand-grasps; in many cases it is confined to this part, but this feature, characteristic as it is, has been given undue prominence in current descriptions of the disease. Hauptmann, for example, is inclined to suspect the diagnosis when active myotonia is present in many muscles other than those of the forearms, but a number of undoubted cases have been described in which many muscles showed this sign. In our patient, J. R., the difficulty in relaxing the grasps, the "buckling up" of the feet on beginning to run, the stiffness in the knees after squatting, and the stiffness in the jaws during mastication, are all expressions of active myotonia. In the patient, W. A., it is demonstrable in all the limb muscles, and in this patient as in others described by Tetzner [56], Rohrer [46], and Rülf [49], the impression was gained that all the muscles of the body were more or less myotonic.

Hence, whilst it is true that active myotonia is most obvious both to the patient and to the superficial observer in the hand-grasps, we feel sure that a careful consideration of all the symptoms and the application of appropriate tests will disclose the fact that it is of much wider distribution in a large proportion of the cases.

As a rule, the difficulty in relaxing the grasp comes on very gradually, and the patient may be unable to state definitely when he noticed it first; but in our patient, J. R., and in another described by Rülf, the onset was sudden, and the spasm reached a maximum degree at its first appearance.

The delay in relaxation usually diminishes rapidly with each repetition of the movement, so that after several attempts it disappears, but several cases have been described in which it persisted or increased. The trouble is always greatest in cold weather, and emotion plays an interesting part in its production. Thomsen himself referred to the effects of psychical stimuli upon a myotonic patient, and the power of these stimuli to provoke the first and subsequent attacks of muscular spasm in persons

presumably myotonic from birth is exemplified in the cases of Thomsen's disease so admirably described by Rosett [47] in a recent number of this Journal.

That the same phenomenon occurs in the so-called symptomatic myotonia of dystrophia myotonica is shown by the circumstances in which it appeared for the first time in one of our patients (J. R.); here the emotional factor was provided by the desire to excel in an examination in rifle drill for promotion to higher military rank; prior to this ordeal the man had never experienced any difficulty in relaxing his grasp, but at a critical moment the flexors of the forearm went into severe spasm, with the result that he was unable to remove his hand from his rifle for several seconds.

As in Thomsen's disease, the severity of the spasm in these cases depends on the amount of power that is put into the movement. One of our patients told us that he always knew when attempts to demonstrate the myotonic hand-grasp would be successful, but it transpired that what appeared at first to be an inexplicable premonition was merely artfulness on the patient's part; for at times when he was not disposed to encourage curious visitors, he abolished his most interesting symptom by the simple expedient of refraining from exerting the amount of strength which he knew from experience was requisite to elicit it. Still another similarity with Thomsen's disease must be mentioned, namely, the sudden "falling like a log" of which some patients with dystrophia myotonica also complain. Rosett relates that this symptom was first described by Charles Bell in 1837, before Thomsen's disease was recognized as a definite entity, and he records its occurrence in two of his own cases. In three of our patients these falls were a prominent symptom; we attributed them at first to weakness in the thigh muscles, but on consideration it seemed that this should not cause a man walking on level ground or, as in one instance, a sentry standing at his post, to fall "like a log," and we were at a loss for a satisfactory explanation. On learning that these falls occur in Thomsen's disease, however, we concluded that they were an expression of myotonia in this disease as well. We realize that the falls are indeed due to weakness in the thighs in many instances, but we are convinced that this is not the explanation in all. Occasionally, when weakness causes a patient to stumble, the effort to prevent a fall causes a generalized spasm of the muscles, so that the patient lies rigid on the ground and except that consciousness is retained appears to be in a fit. In one case this kind of attack was mistaken for a seizure of general paralysis.

In several of our cases we have noticed that alternating movements, flexion and extension at the elbow, for example, were well done if the patient was allowed to carry them out at his own rather slow pace, but that if he attempted to increase their rate they became grossly incoordinate, the most obvious defects being that one movement, say extension, was begun before flexion was completed, and vice versa, and that adventitious movements were made at the shoulders and wrists, so that after a number of repetitions the arms were flung about in a most disorderly fashion, the desired movement of flexion and extension being but little in evidence. This phenomenon finds a ready explanation in the myotonia of the muscles involved; when the movements are carried out slowly one group of muscles has time to relax before contraction begins in the other; but when the patient attempts to increase their rate, in the first place he exerts greater force, so that myotonia is more likely to appear, and in the second relaxation is not complete in one group before contraction begins in the other. Rosett has shown in cases of Thomsen's disease that if a stimulus to myotonic muscles, be it mechanical, electrical or volitional, is repeated rapidly, a summation of residual contractions occurs; it may be then that in our cases as well, after several repetitions of flexion and extension, the muscles concerned in these movements, agonists and antagonists alike, go into continued contraction, so that ultimately neither flexion nor extension is possible. But the patient is still exerting himself, and an overflow occurs to muscles moving other joints, so that irregular adventitious movements occur.

Having drawn attention to these expressions of widespread myotonia it is perhaps necessary to repeat that, although this symptom may be demonstrable in many muscles, it is true that in the great majority of the cases it is *obvious* in the hand-grasps alone.

Contrasted with the limited distribution of obvious active myotonia, persistence of contractions produced by percussion of the muscles—mechanical myotonia—is usually more widespread. It is most constant in the tongue and in the small muscles of the thenar and hypothenar eminences, but it is often present in many other muscles as well. In the tongue it is sought for by striking the lateral border with a small percussion hammer; when it is present a deep dimple forms at the point of impact and persists for several seconds; in the hands it is even more easily demonstrated because the prolonged contraction of the muscle is associated with obvious and prolonged displacement of the thumb or little finger, according to the part that is struck. In larger

muscles the characteristic myotonic response to mechanical stimulation is the formation of a persistent furrow deepest and broadest at the point of impact. Mechanical myotonia, like other forms of myotonia, varies greatly in the extent of its distribution in different cases, and it shows great variations in the same case at different times.

It is always most obvious in muscles showing little atrophy or none at all, and it is rarely found in wasted muscles; but this cannot be accepted as evidence of an antagonism in distribution between atrophy and mechanical myotonia as some have held, for we have frequently seen mechanical myotonia in the as yet unwasted muscles in parts where atrophy is common. We find the explanation of the apparent antagonism in the fact that mechanical myotonia disappears when atrophy supervenes. When atrophy is absent in muscles where it commonly occurs, these muscles are frequently myotonic; in cases with atrophy in the usual situations myotonia is absent in the wasted muscles but is found in muscles free from atrophy; in advanced cases when all the muscles are wasted, mechanical myotonia may be nowhere demonstrable.

Before leaving this subject something must be said of a kind of persistent contraction after mechanical stimulation which has nothing to do with myotonia. The normal response to mechanical stimulation is a contraction of short duration in the long axis of the fibres beneath the point of impact; now it often happens that, as the fibres relax in parts remote from the point of impact a prominence appears at this point, and after persisting for several seconds disappears slowly; this can be observed most easily in the pectoral muscles, but may be present in many others; the duration of this localized transverse swelling is often just as great as the persistent contraction of myotonic muscles, and may cause confusion, but error will be avoided if it is remembered that the true myotonic reaction appears in the form of a dimple or furrow, not as a prominence.

It has been stated that the normal myotatic irritability of the muscles is abolished in this disease. In a number of our cases we have investigated the response to mechanical stimulation in all the accessible muscles, and we have been struck by the frequency with which such stimuli failed to produce a response of any kind in muscles that seemed to be healthy in other respects; nevertheless, normal responses were often obtained, and in several cases percussion of the pectoral muscles evoked a typical "harp-string response" (Oppenheim) which did not differ in any respect from that seen in normal individuals.

Electrical Reactions.

The electrical reactions in this disease show many deviations from the normal; the quantitative changes are those that we expect to find in muscular atrophy of myopathic origin; the qualitative changes are identical in nature with those that occur in the myotonic muscles of patients with Thomsen's disease, but are often modified by the presence of atrophy in the myotonic muscles. In weak muscles and muscles showing active or mechanical myotonia, the reaction to direct faradic stimulation is often diminished; as a rule the reaction to indirect faradism is normal, but when atrophy is severe this is also diminished; to direct galvanism the excitability of the atrophic muscles is sometimes increased, but it is more often diminished. In many respects the reactions resemble the reaction of degeneration, for apart from the changes just mentioned A.C.C. is often greater than K.C.C. and slow worm-like contractions are sometimes observed on direct galvanic stimulation; indeed the earlier writers described their findings as a combination of the myotonic reaction with the reaction of degeneration. Steinert and Curschmann, however, pointed out that the slow contractions only occurred on closing the current, whereas anodal opening contractions were prompt; that even the closing contractions become normal on repetition of the stimulus, that slow contractions may occur on direct faradic stimulation also, and that the muscle is usually excitable through the nerve. Their conclusion was that the changes were merely deviations of the myotonic reaction due to the presence of atrophy in the muscles and that they differed fundamentally from the reaction of degeneration. With this view almost every subsequent observer has concurred, and we may safely conclude that the reactions in this disease, however closely they may resemble it, have nothing to do with the reaction of degeneration whatsoever.

In most cases the classical myotonic reaction is found in very few muscles or in none at all, but it is usual on the other hand to find changes in many muscles which may be looked upon as minor modifications of it. In some cases no normal twitches can be obtained from some of the muscles by direct galvanic stimulation, for even with minimal current strengths the muscle goes into a prolonged tetaniform contraction; this constitutes Remak's "incomplete myotonic reaction." In others galvanic and faradic stimuli of short duration evoke normal twitches, but if the stimulus is prolonged, the strength remaining the same, a myotonic after-contraction occurs (Steinert-Pässler phenomenon). This type of reaction was present in two of our cases; in some muscles

the contraction persisted as long as the current was passing and relaxed promptly as soon as it was withdrawn, in others relaxation was slow; with the galvanic current this phenomenon occurs more readily from the anode than from the cathode. In cases described by Steinert, Hauptmann, Baake and Voss, and Maas and Zondek, no response was obtained from some of the muscles with currents of minimal strength, but when the stimulus was greatly prolonged the strength remaining the same, the muscle went slowly into continued contraction and then relaxed slowly after the stimulus was withdrawn. This type of reaction was seen in one of our patients; we observed that during the slow inception of the muscular contraction the galvanometer needle was rising and that as long as the needle remained steady the muscle remained in "galvanotonus." We concluded therefore that the phenomenon was due to "galvanotonus," and that the appearance of the slow contraction was due to a gradual diminution in the resistance of the skin. Many other modifications of the classical myotonic reaction have been described, indeed it seems as if every observer who directs his attention to the electrical reactions in these cases finds something that has not been described before, but it is not yet possible to say whether any one of them is constant or peculiar to this disease.

We have said that myotonia is the most constant symptom of the disease; we must now consider the cases in which it was said to be absent.

Under the heading "Dystrophia myotonica sine myotonia," Curschmann [10] has described a family consisting of three brothers and a cousin; the patients showed muscular atrophy of typical distribution, cataract, atrophy of the testicles, impotence, baldness, loss of reflexes, hypersecretion of sweat and other characteristic symptoms, but in two of them myotonia was completely absent and in another it was present in a minimal form as mechanical myotonia in the tongue and thenar muscles alone. There is no doubt about the diagnosis in these cases, as the patients with and without myotonia but with other symptoms in abundance were brothers. Rohrer has described two cases in which myotonia was absent. In one, a man aged 53, the findings were: atrophy of the forearms, face, sternomastoids, temporals and legs, presenile cataract (operation) at the age of 40, baldness, impotence, general loss of body weight and other less definite symptoms; no myotonia, no history of muscular disorders or of cataract in other members of the family. In the other case, a woman aged 39, the symptoms were atrophy of the forearms and face, presenile cataract

and certain indefinite dystrophic symptoms; no myotonia and no family history. In many respects these cases are typical enough, but we hesitate to accept them, as confirmation of the diagnosis from the family history is lacking. Until special investigations have shown that cataract does not occur in other muscular dystrophies, we cannot agree that the combination of presenile cataract with muscular atrophy but without myotonia justifies a diagnosis of dystrophia myotonica, although it makes it highly probable. It might be said that in Rohrer's cases the diagnosis is confirmed by the presence of other dystrophic phenomena, but we do not attach much importance to these in doubtful cases, firstly because it has not been shown that they do not occur in other muscular dystrophies, and secondly because the enthusiastic investigator of the ductless glands rarely fails to find evidence of some disorder in their supposed functions in any given case.

In one of Fleischer's cases there is no account of myotonic symptoms, but as the electrical reactions are not given, and as electrical myotonia may be present alone, the case is not acceptable for our present purpose. In some of Batten's original cases too, myotonia was said to be absent, but the investigations, according to modern standards, were incomplete. Against Curschmann's cases, however, there is nothing to be said; they prove that myotonia may be completely absent in isolated cases *at the time of examination*, but they do not permit us to assume, as Curschmann, Rohrer and Naegeli have done, that it may be absent in certain cases throughout the course of the disease, nor do they justify the contention that myotonia is merely an occasional and unessential symptom of subsidiary importance.

Myotonia is notoriously variable in distribution and intensity in the same case at different times; it tends to disappear in the advanced stages when atrophy is severe and general, and it may be absent at one time and present at another, as is shown by the case reported by Niekau [42] as an example of "dystrophia myotonica sine myotonia" which was recognized by Slauck [52] as one that had been under his observation on four occasions when myotonia was always present: we are prepared then to encounter cases in which myotonia is absent at the time of examination, but nothing that we have learned in our study of the disease leads us to associate ourselves with those who hold that it may be absent throughout its course.

Further, with regard to the diagnosis in cases free from myotonia, it must be remembered that the isolated cases in which it was absent stand alone amongst the hundreds in which it was present in some

degree; hence we consider that the greatest caution should be exercised before cases without this symptom are admitted to our category. For the present at least we should use the family history as our criterion and withhold the diagnosis in doubtful cases unless the occurrence of characteristic cases in other members of the family supplied the necessary confirmation.

We do not intend to enter upon a discussion of the theory of myotonia in general, but as our electro-myographic investigations have a bearing on this subject it must be mentioned briefly. The earlier writers on Thomsen's disease were satisfied that myotonia was of myogenic origin; during recent years, however, several observers have supported a neurogenic theory. (Curschmann [9], Albrecht [2], Stocker [55], Gregor and Schilder [17].)

Gregor and Schilder working with the string-galvanometer on cases of dystrophia myotonica found during the myotonic after-contraction oscillations with a fifty per minute rhythm, which they therefore regarded as evidence of a central origin for the myotonia. These authors look upon the myotonic reaction as a proprioceptive reflex—the voluntary contraction produces a stimulus in the muscle itself which calls forth another contraction through the reflex path and so on. Schäffer [50] in a recent paper disagrees with Gregor and Schilder's conclusions and upholds the myogenic theory; he failed to find oscillations suggestive of a neurogenic origin for the myotonic after-contraction in cases of Thomsen's disease, and they were certainly absent in our case of dystrophia myotonica; Schäffer showed too that myotonia persists when the nerve endings in the muscles are paralysed with novocain and when the nerves to the limbs are paralysed by regional anæsthesia. Grund [21], moreover, had previously reported that it persisted in limbs paralysed by intrathecal injection of stovaine. This work suggests that the myotonia of Thomsen's disease is myogenic in origin, and our own limited observations lead us to conclude that the same is true for the so-called symptomatic myotonia of dystrophia myotonica.

Muscular atrophy.—Our knowledge of the distribution of the muscular atrophy in this disease has passed through several distinct phases. The earlier writers, Hoffmann [29] for example, saw nothing distinctive in it and commented upon its apparent irregularity. Batten and Gibb on the other hand suggested that "a characteristic distribution may exist in this disease" and by neglecting the cases in the literature that differed from those that had come under their

own observation they were able to differentiate a distinct clinical group in which weakness was confined to the facial muscles, the muscles of mastication, the sternomastoids, the vasti of the thighs and the dorsiflexors of the feet. According to Steinert, who had reached the same conclusion independently, three stages could be recognized in the spread of the atrophy: the muscles of the forearms are first attacked, then those of the face, the sternomastoids and the muscles of mastication; at a later stage atrophy spreads from these sites of predilection and many other muscles are affected; the peronei, he added, might be attacked at any stage. Batten and Gibb based their conclusions on the findings in twenty cases; subsequent observations on hundreds of others show how well they attained their object which was "not so much to discuss the whole subject of myotonia atrophica as to suggest the possibility of there existing a form of myopathy differentiated clinically from the classical type as much by the distribution of the wasting as by the presence of the myotonia," for in a majority of cases the distribution of the atrophy conforms to Batten's description; his precise delineation of the features of characteristic cases served its purpose admirably, and, supported by Steinert's findings, it led quickly to the recognition of these cases as a distinct clinical group. But all cases do not conform to these classical descriptions, which apply to a type only, and it remains for us to indicate the variations that may occur. Our conclusions are based on an analysis of 123 cases in which we were satisfied that the diagnosis was correct.

Weakness always appears first in one of the following situations: the facial muscles, the muscles of mastication, the sternomastoids, the forearms, the vasti of the thighs or the dorsiflexors of the feet; it is usually present in more than one of these groups when the patient first comes under observation but it may affect any one of them first, or most, or alone.

The sequence described by Steinert is certainly not constant, nor is it the most frequent, for our figures show that the forearms are spared in many cases when atrophy in some or all of the muscles of the head and neck group is severe. Our Case 2, with extreme atrophy of the sternomastoids without weakness or wasting in the forearms, illustrates this, and cases with little or no wasting in the forearms with severe atrophy in the head and neck muscles have been described by Batten, Tetzner, Curschmann, Kramer, Bramwell and Addis, Rohrer, Hauptmann and others. On the other hand, atrophy of the forearms alone is rare.

Within the head and neck group it is usual to find some weakness of all the muscles, but one pair often suffers more than another and atrophy may be extreme in one, in the sternomastoids for example, before the others are attacked. Absence of demonstrable weakness in the orbicularis oculi seems to be the rarest negative finding; even when this is absent the face is usually described as being "expressionless and immobile"; absence of weakness in the sternomastoids is next in order of rarity. The muscles of mastication usually succumb early; the wasting is always most obvious in the temporal muscles, where it may be extreme before the bulk or power of the masseters is diminished, and the resulting temporal hollow aids materially in producing the characteristic facies of the disease; dislocation of the jaw as a consequence of weakness in these muscles was noted first by Nolne; it occurred in two of our cases. In the forearms the supinator longus is picked out first and it may waste greatly before other muscles in the forearm group are attacked (Steinert, Tetzner, Hauptmann).

It has been said that the extensors are always more affected than the flexors, but our observations suggest that no rule can be given on this point; we have seen several cases in which the flexors suffered most and the same has been noted by Grund, Hauptmann and others. Weakness and wasting of the dorsiflexors of the feet is mentioned in less than half of the cases in the literature, but if our remarks had been founded upon our own observations alone we should have placed the incidence of weakness in this group at a much higher figure. If the lower limbs are attacked at all these muscles or the vasti of the thighs always succumb first; in many cases weakness in the legs has been the first symptom and in some dropped foot and great difficulty in walking were obtrusive symptoms when power in the upper limbs was still good.

From the sites of election already mentioned atrophy may spread to adjacent muscles, or pick out individual muscles at a distance in an order for which we can find no rule; if we were to give priority to any muscles outside the classical situations, we should mention the small muscles of the hands, the deep neck muscles, and the muscles of the upper arms and thighs. In many cases some of these are attacked before atrophy has appeared in all the sites of predilection; for example, when atrophy in the forearms is severe the small muscles of the hands or the muscles of the upper arms may waste before the legs are affected, but no case has been described in which atrophy appeared first in a muscle outside the main groups. The rate at which atrophy

progresses is extremely variable; it may be severe and widespresd a year after the appearance of the first symptom, or it may be minimal in most of the muscles many years after the onset of the disease; in one of our patients with wasting of the sternomastoids and facies myopathica the limbs retain their bulk and power seven years after the onset. In some advanced cases every muscle in the body is wasted, in others of equally long duration the trunk muscles and the muscles of the shoulder and pelvic girdles retain their bulk.

As in other types of myopathy, the loss of power in some of the muscles is often greater than the degree of atrophy would suggest; pseudohypertrophy is said to occur in rare cases, but a special study of the recorded cases leaves us in doubt upon this point, as we are inclined to attribute the apparent hypertrophy to the striking contrast in the size of muscles free from atrophy with those that have wasted. Batten described hypertrophy of the muscles below the knee in one of his cases, but the vasti were completely atrophied; in a case described by Griffith, the calves were said to be hypertrophied but their circumference was only 14½ in. and the patient had been a footballer. Slauck mentions that he has seen a case with marked hypertrophy of the quadriceps of the thigh. Mendel demonstrated a case at a clinical meeting in Berlin with typical myotonic symptoms, severe atrophy of the forearms, arms, infraspinati and sternomastoids and "great hypertrophy of the thenar and hypothenar eminences and of the calves," but as there was no facies myopathica, and as extra-muscular symptoms seem to have been absent, the diagnosis is doubtful; we have seen one case that had previously been under the care of two of our colleagues who had both described it independently as one of "myotonia atrophica with pseudohypertrophy"; the contrast between the size of some of the wasted and unwasted muscles was certainly very great, but it was doubtful whether the larger muscles were really hypertrophied. Be this as it may, it is certain that some of the muscles may appear to be unduly large and that these muscles are often extremely weak.

Atrophy of the tongue has been recorded by Grund and Steinert; it was present in two of our cases, but it is uncommon and is always slight in degree.

In two cases described by Albrecht [3] the soft palate was "as thin as paper" and the œsophageal walls were thin and very lax. Various paralyses of the vocal cords have been observed (Nonne [43], Batten [4], Siemerling [51], Bramwell and Addis [7], Albrecht [3], Tilley [57] and others).

Fibrillary tremors identical in appearance with those seen in atrophies of spinal origin were present in the thigh muscles of the patient, W. A., on several occasions; they were seen in one case by Batten and in another by Fuchs, but they were almost certainly fortuitous and all writers agree that they are foreign to this disease.

In certain cases, few in number but of great theoretical interest, muscular atrophy was entirely absent. Case 1 (Rohrer): a woman of 35, with presenile cataract, typical myotonia, expressionless face, nasal voice, no family history. Case 2 (Rohrer): a woman of 36, with typical myotonia, monotonous voice, presenile cataract; two sisters and two brothers suffer from the disease in its most typical form.

Case 3 (Fleischer): a man of 27 with typical myotonia, and incipient cataract; his brother is a typical case. Case 4 (Fleischer): a man of 25 with typical myotonia, apathetic expression, presenile cataract, scanty hair, no family history. Whatever may be thought of the cases in which confirmation of the diagnosis from the family history was lacking, the others prove that the disease sometimes occurs in an incomplete form, and that other symptoms may betray its presence when muscular atrophy is absent. Fleischer's patients were still young and it may be that atrophy will occur later, but both of Rohrer's patients had passed the age at which atrophy usually begins.

So far we have concerned ourselves with the incidence and spread of muscular atrophy; we must now consider its nature. In one particular alone, namely its predilection for the extremities of the limbs, it differs from the better known progressive atrophies of myopathic origin, but in every other respect they are identical; the electrical reactions, apart from the complications introduced by myotonia, are the same; fibrillation is foreign to both, weakness is often great in muscles that have retained their bulk, no changes have been found in nervous structures to account for the weakness and wasting, and, most important of all, the histological changes in the muscles in both conditions are the same and they differ fundamentally from those that occur in atrophies of nervous origin. The morbid appearances in the muscles of four of our patients are described on another page; our findings agree in every detail with those of Slauck [53], whose recent paper came to our notice after the completion of our own pathological investigations; this observer made a special comparative study of the changes in dystrophia myotonica and other progressive myopathic atrophies and found that the agreement was "overwhelming." We may conclude then that the changes in the progressive dystrophies and in dystrophia myotonica are

of the same nature, and that in the one as in the other they are, so far as we know at present, myopathic in origin. In other words, the atrophy is not neurogenic in the ordinary sense and does not depend upon a lesion of lower motor neurone. But this does not exhaust the possibilities of a neurogenic origin, for it has been suggested that the atrophy may be due to the loss of a hypothetical trophic influence that normally reaches the muscles through sympathetic fibres. This hypothesis has received warm support from Naegeli and his co-workers, who maintain that the primary defect in this disease is a "pluriglandular disorder of internal secretion"; to explain the muscular symptoms they assume that the functions of voluntary muscles can be influenced through the sympathetic system and therefore indirectly by the ductless glands; striped muscle, they say, identifying themselves with the views of Frank [13] and others, has a double innervation by ordinary motor fibres which supply the fibrils, the part of the muscle concerned in phasic contractions, and by sympathetic fibres which supply the sarcoplasm, the part of the muscle concerned with tonic contractions, and it is to disturbance in the innervation of the sarcoplasm that atrophy and myotonia in this disease are said to be due. A discussion on this alleged dual innervation of the somatic musculature would be out of place here, but as explanations of many obscure phenomena of nervous disease have been based on the assumption that the sympathetic nervous system has an influence on the tone and nutrition of voluntary muscles, we think it should be stated that competent observers in increasing numbers have protested against the unwarranted conclusions to which the possible existence of sympathetic endings in striped muscle have given rise. In the words of one highly qualified observer, the whole subject "still remains within the realms of pure fantasy," and there are many who agree with him. Be this as it may, we must admit that a neurogenic origin for the muscular atrophy in dystrophia myotonica is as yet "not proven," and that in the present state of our knowledge we must look beyond the ductless glands for its cause.

(3) *Cataract.*

Among the many extra-muscular symptoms of dystrophia myotonica cataract holds the place of first importance, not because of its frequency —it occurs in less than half of the cases—but because of the decisive part it has played in the development of our knowledge of the disease as a whole. Its occurrence in this disease was described for the first

time by one of us [16] in 1911. In the same year cases were reported by Kennedy and Oberndorf [34], and Ormond [44], and since then others have been described by Kennedy [33], Hoffmann [30], Curschmann [8], Löhlein [38], Hauptmann [24], Rohrer [46], Fleischer [12], Rülf [49] and others.

This curious combination of degenerative changes in structures so dissimilar as lens and muscle at once arrested attention. Greenfield [16] in his original paper was the first to suggest that "the degenerative conditions in the lens and muscles may be due to a deficient vitality on the part of the tissues showing itself in these somewhat specialized structures." In 1912, Hoffmann [30] reviewed the published cases and expressed the opinion that cataract and myotonia atrophica were intimately connected; in the same year, Curschmann [8], seeing in the association of cataract with the other extra-muscular symptoms evidence of a general intoxication, rejected all the pre-existing myogenic theories of the disease, and formulated the hypothesis that it is due to a disturbance in the organs of internal secretion or of the central nervous mechanisms that control them.

Subsequent observations on the incidence of cataract have further enhanced its significance, for increasing knowledge has shown that the other remarkable features first exemplified in Greenfield's family are also characteristic of the disease; we refer to the occurrence of cataract in the otherwise healthy brothers and sisters of patients with dystrophia myotonica, and in otherwise healthy members of earlier generations of the afflicted families. In Greenfield's family five members in the same generation suffered from dystrophia myotonica, two with and three without cataract, and two from cataract alone; a paternal aunt and grandfather also had cataract.

In a family described by Hoffmann, dystrophia myotonica with and without cataract, as well as cataract alone, was found in the dystrophic generation, and a grandfather had cataract. Following these observations, the occurrence of uncomplicated cataract in the brothers and sisters of dystrophic patients was noted with increasing frequency and was soon accepted as one of the features of the disease. With regard to cataract in earlier generations, however, the number of observations remained small (Greenfield, Ormond, Hoffmann); no one ventured to suggest that it was more than a coincidence and no material addition to our knowledge of this aspect of the subject was made until 1918 when Fleischer [12] published a remarkable account of thirty-five cases of dystrophia myotonica with cataract that had come under obser-

vation in the eye department of The University Hospital at Tübingen. Fleischer's patients were distributed over twenty-seven families; in eleven of these one of the otherwise healthy parents of children with dystrophia myotonica had cataract, and uncomplicated cataract occurred frequently in the brothers and sisters of the parents and in members of earlier generations.

In one remarkable family, for example, where three brothers and sisters were the parents of children who developed the disease, these three, their younger brother, a sister of the grandfather and a daughter of his sister, as well as the common ancestor, the great-grandfather of the dystrophic generation, all had cataract but were otherwise healthy. To Fleischer's eleven families with uncomplicated cataract in earlier generations we can now add one of Curschmann's [10] with cataract in three members of the dystrophic generation, in four of the preceding generation, and in one of the generation before this.

With all this evidence before us, then, we may now conclude that cataract in earlier generations is also one of the characteristics of the disease. So far we have used the term cataract without qualification; its characters, however, are not the same in the different generations; in patients with dystrophia myotonica and in their brothers and sisters, cataract, if it occurs at all, appears at an early age; in the members of the preceding generation it appears later but is still presenile in most instances, whilst in earlier generations it comes on in old age as ordinary senile cataract.

This remarkable "anticipation" was evident in twelve of Fleischer's families, and is well illustrated in one where cataract occurred in different members of the dystrophic generation at the ages of 27, 30, 31 and 40 years, and in the preceding generation at the ages of 37, 38, 52, 56 and 65 years, whilst a member of the generation before this and his father had ordinary senile cataract. In Curschmann's family the ages were 38, 42, 44 and 47 in the dystrophic generation and 50, 50, 78 and 80 in the preceding generation.

In its typical form the presenile cataract of the dystrophic generation begins as a star-shaped opacity first in the posterior and then in the anterior cortical lamellæ, with or without very fine punctiform opacities scattered throughout the lens. It ripens quickly to a total soft cataract with a small nucleus, at about the same time in both eyes. In the preceding generation its characters are much the same except that consistent with the more advanced age at onset the nucleus is larger and harder. In earlier generations it comes on in old age and has the characters of ordinary senile cataract.

It is not yet possible to say in what proportion of cases cataract occurs; it may be symptomless and, as it is only recently that a special examination of the lens has formed a part of the routine examination of these cases, most of the older reports are valueless for statistical purposes.

The difficulty is still greater in the case of the earlier generations because patients often know very little about their relatives and the opportunity for examining more than a few of them is rarely obtained. Ten years ago Hoffmann estimated that 10 per cent. of patients with dystrophia myotonica also had cataract; Curschmann's estimate (1922) is 30 per cent.; time may show that it is even higher than this.

Of Fleischer's thirty-eight cases with cataract twenty-four were women; this is surprising because the incidence of the disease according to collected statistics is greater in males in a proportion of five to one. Further, most of his patients between the ages of 25 and 35 years were women, whilst those between 35 and 45 were men; and as the other symptoms—muscular atrophy and myotonia—were always found with the cataract his cases seem to prove that cataract is commoner in women, and that not only cataract but also the disease itself appears at an earlier age in this sex.

Some additional points regarding the incidence of cataract will be considered when we come to discuss dystrophia myotonica as a heredofamilial disease.

(4) *Other Dystrophic Symptoms.*

Atrophy of the testicles was noted first by Fürnrohr [15]; next to baldness it is perhaps the most frequent extra-muscular symptom. Its value as an objective sign is not great, as the size and consistence of the testicles varies so much in normal persons, and its presence or absence in a given case will depend on the observer's idea of the normal. There is no doubt, however, that the sexual functions are affected sooner or later in a very large number of cases of both sexes, and it is reasonable to connect the almost constant loss of desire and power in males with changes in these organs. The statement is often made in case reports that the patients have never had intercourse; in some the external genitals remain infantile; celibacy and childless marriages are common. More often the sexual life is normal up to the age of 25 or 30 with normal procreative powers; then as the disease develops desire and power disappear. One of our patients begat a healthy child at the age of 30, four years after the onset of the disease.

Baldness, especially in the frontal region, is very frequent, and in some cases the growth of hair on other parts of the body is scanty. A general wasting of all tissues of the body and a loss of body weight much greater than can be accounted for by muscular atrophy is seen in many cases. It has been stated that this is due in part to a diminution in the calcium content of the bones, and it is probable that this defect plays a part in the production of the spinal and other bony deformities that are sometimes present in advanced cases.

Increased secretion of sputum, sweat or tears, has been a symptom in a number of cases. (Ortleb [45], Hauptmann [25], Curschmann [8] and others). Hauptmann attaches particular importance to this group of symptoms as he sees in it evidence of a disorder of autonomic innervation. In two of our cases we thought at first that the forehead was constantly covered in sweat, but closer observation showed that the moist appearance was due to an excess of natural grease. We have never seen a case in which the secretion of sputum or sweat was increased; in two cases the eyes watered readily, but whether this was due to lagophthalmos or to excessive secretion of tears we are unable to say.

The effects of injections of substances which are supposed to be of value in revealing the state of the autonomic and sympathetic nervous systems, as pilocarpin, atropin, adrenalin, have been investigated in a number of cases with contradictory results. Excessive reactions to pilocarpin have been noted by Hauptmann [24] and Fünfgeld [14], but in one of our cases susceptibility to this drug seemed to be diminished rather than increased; it is certain that these reactions, even if they mean anything, are not constant in this disease and further investigations are necessary before it can be said that they are frequent. Details of the methods in use are given in an article by Fünfgeld [14].

Other occasional findings that have been recorded as evidence of disorder of the ductless glands are: increase in the relative number of lymphocytes in the blood, eosinophilia, increase in the coagulation time of the blood, increase or diminution in the size of the thyroid gland, vasomotor disturbances, especially cyanosis and coldness of the extremities (whatever its significance, this symptom is certainly common), increased irritability of the facial nerve, and others which are supposed to indicate vagotonia or sympatheticotonia.

All these minor signs have been present in some cases and absent in others, just as they would be in the same number of individuals either healthy or suffering from some other disease, and as it is more

than probable that the whole subject of the relation of the ductless glands to the sympathetic and autonomic systems will soon be subjected to drastic revision we do not consider that it is profitable to discuss these symptoms in further detail.

Tabetic symptoms.—Loss or diminution of the tendon reflexes in the upper and lower limbs has been noted in a large number of cases; indeed it is extremely rare for all of them to be present. That this should occur when atrophy of the muscles is severe is not surprising, but it often happens that the knee-jerks, for example, are absent when the muscles concerned appear to be healthy. A ready explanation for this was found in the degeneration of the posterior columns described by Steinert in his case which remained for many years the only one that had been examined after death; but this degeneration was absent in all the cases that have come to autopsy recently, and it seems as if the cause for the loss of reflexes must be sought in the muscles themselves.

Objective sensory disturbances were present in the lower limb in one of Curschmann's early cases, but this has never been found since and we can safely conclude that it was fortuitous. On the other hand, subjective disturbances, in the form of severe pains in the lower limbs, have been described in many cases, particularly about the time of onset of the disease, as in one of our cases and in others described by Batten, Hoffmann, Rossolimo, Curschmann, Rohrer and Rülf.

The peculiar gait of some of the patients with this disease has also been included amongst the so-called tabetic symptoms. The patient fears sudden falls and therefore walks carefully on a rather wide base; weakness of the leg muscles and a tendency to dropped foot introduces a steppage element; the extensors of the neck are weak and the head inclines forward so that the eyes appear to be directed towards the ground, and altogether the resemblance to the gait of some tabetics is a close one but it is entirely superficial.

Romberg's sign has been described in one or two cases, but seeing that sensory disturbances are never present, its significance cannot be the same as the true Rombergism of tabes. Sphincter disturbances were noted in several cases but only in the terminal stages of the disease.

Other symptoms.—Considerable attention has been given to the psychical changes in this disease, but it cannot be said that any particular change is constant or characteristic. As all the patients have belonged to the lower classes it is perhaps not surprising that their

intellectual attainments have not been high; all our male patients had earned their own living, some of them in trades that demanded a considerable amount of intelligence. In many cases, however, the temperament shows a peculiarity that is rather difficult to define; dulness and lack of interest are perhaps more apparent than real in the majority of cases, as the expressionless face is apt to be misleading.

It is often very difficult to elicit the facts of the family history and sometimes it seems as if they are withheld voluntarily; the patients are often suspicious and mistrustful, resenting examination and refusing to submit themselves to special tests; they leave hospital without warning before the physical examination is completed and they cannot be trusted to present themselves for exhibition at a time that had been arranged. As a rule they are selfish, unsociable and difficult to manage, but they are cunning and shrewd and well able to look after their own interests; some of our patients on the other hand were pleasant individuals, entirely free from psychical defects and peculiarities of temperament.

Speech is nearly always affected. The voice is low, it lacks intonation and has a more or less definite nasal quality. These defects have been attributed to muscular atrophy and to myotonia; perhaps both play a part, as the lips, tongue, soft palate and vocal cords are often weak, and the tongue and perhaps other muscles as well are frequently myotonic.

Stigmata of degeneration are often present. We have been struck by the almost constant presence of a very high, narrow, hard palate in these cases.

Extreme slowness of the heart has been observed in isolated cases (Rohrer, Griffiths, Maas and Zondek).

Maas and Zondek [39] have described three cases in which they found a dilated heart and a definite increase in the As-Vs interval in electro-cardiographic tracings. This observation lacks confirmation; in the one case that we have examined electro-cardiographically the time relations of the events in the cardiac cycle were normal.

IV.—Heredo-familial Features.

In 1916, Rohrer made an analysis of the published cases of dystrophia myotonica and found that it was familial in forty-three cases and non-familial in forty-nine, whereupon he subscribed to the prevalent opinion that the majority of the cases are non-familial. This notion, that in certain diseases some of the cases are familial and others not, is one

with which we are familiar, and Rohrer's figures might have served to perpetuate it; fortunately, however, they have been refuted by Fleischer, who has shown that in dystrophia myotonica at least every case is familial, and his work suggests that the same is true for other familial diseases in which isolated cases are supposed to occur. This observer made *ad hoc* examinations of all the available relatives of his patients and undertook the laborious task of tracing the records of his families through many generations in the church registers. His thirty-eight cases were distributed over nine stocks; twenty-nine of the cases were obviously familial, as other children in the family were affected, and in four others the heredo-familial factor was shown in the presence of presenile cataract in one of the parents, so that only five cases remained in which no family history was obtained. In these the investigations were incomplete, or the patients had disappeared, and their families could not be traced. In two families, brothers and sisters alone were affected; in one family three brothers and sisters who had cataract but were otherwise healthy transmitted the disease to some of their offspring; in one family the affected members in two branches had a common great grandfather; in two unrelated families the affected children in two branches of each had a common great-great-grandfather; in two other unrelated stocks, the relationship of the affected members went back to a common great-great-great-grandfather.

Fleischer's figures contrast strongly with those of Rohrer and must be accepted as proof of the contention that when a family history cannot be obtained, it is much more likely that the investigations are incomplete than that the case is non-familial.

It is easy to understand, on the other hand, why so many apparently non-familial cases have been reported. In the first place, the patient's statement that no other member of his family is similarly affected is often accepted as true; but these patients are notoriously untrustworthy on this point, and they often give the impression that they withhold information purposely, sometimes for obvious reasons connected with claims for compensation or pensions, sometimes for no discoverable reason. Hauptmann, one of the first writers to insist on the invariable familial nature of these cases, has discussed these difficulties, and everyone who has had dealings with these patients must have encountered them. An excellent example is furnished by Bramwell [6], who relates that one of his patients went so far as to deny that he had any brothers and persisted in his denials until he was confronted with a photograph of himself and two brothers that had been taken at the hospital

some years before. Again, patients of the class in which this disease occurs often know very little of their relatives, especially of their cousins and more distant relatives of the same child rank as themselves, that is in just those members in whom the disease is likely to occur; further, the disease manifests itself during a short period of life only, and a patient who has perhaps known a cousin as a healthy young adult may well be unaware of the affliction that has come upon him later in life. Another difficulty arises from the fact that one or two children alone may be affected in a large family; one child in eight, one in nine, two in fourteen, two in twelve, two in eleven was the incidence in certain families.

But even when one child alone is attacked it is not justifiable to conclude that the case is non-familial, for in one of Fleischer's families, in which one child in eight was affected, the familial factor was disclosed when it was discovered that this patient and another apparently non-familial case had a common great-great-grandfather. In the face of evidence such as this few will have the temerity to maintain that any isolated case of dystrophia myotonica or indeed of any other familial disease is in reality non-familial, and most will be prepared to acknowledge the truth of Hauptmann's dictum that if a family history is not forthcoming either the diagnosis is incorrect or the investigations are incomplete.

Perhaps the most remarkable fact that has been brought to light by Fleischer's genealogical studies is this, that the disease may be transmitted latently through as many as six generations to burst forth suddenly in a number of families at the same distance from a common ancestor. Transmission seems to take place through males and females indiscriminately, but the fully developed disease is more frequent in males. It seems to us, too, that the syndrome we call dystrophia myotonica is confined almost entirely to one generation. The mother of one of Batten's patients had "difficulty in letting things go" all her life, but no account of other symptoms was obtained, and she attained the age of 82, which is almost double the age that has ever been reached by any patient with the fully developed disease. The father of Tetzner's patient had "wasting of the muscles." One of our patients told us that his father "always slept with his eyes open," but was "very healthy and strong." The father of one of Curschmann's patients "walked unsteadily and his speech was indistinct." Four uncles and aunts and the grandfather of one of Rohrer's patients were said to be affected with the same disease, "it ran in the family." We have

collected several more similar observations, but in almost every other case report it is stated definitely that the parents and other relatives of earlier generations were free from symptoms suggestive of the disease. Fleischer's records are of the greatest value because particular attention was paid to this point, and his conclusion is that the occurrence of dystrophia myotonica in the ancestors of his patients was not only never proven but was not even probable in a single instance. The rule, however, is not absolute, for Grund [20] has described a mother and two sons who suffered from the disease in a typical form, and Curschmann [8] found it in a father and son. In the present state of our knowledge, then, it seems as if the position is that in the great majority of cases the parents of the dystrophic generation are healthy (apart, of course, from the frequent occurrence of presenile cataract), that in certain instances, as in the one case where the absence of closure of the eyelids during sleep may be accepted as evidence of weakness of the facial muscles, and in Batten's case, where myotonia was almost certainly present, the parents of the dystrophic generation may present some of the features of the disease, whilst in isolated instances the fully developed disease occurs in members of more than one generation.

It is perhaps too early to say that the disease dies out, as it seems to do, with the generation in which dystrophia myotonica occurs; records exist, however, of about one hundred children and of a number of grandchildren of dystrophic patients, and none of these, apart from the exceptional cases of Grund and Curschmann, has shown any sign of the disease.

But although the syndrome that we call dystrophia myotonica seems to be confined almost entirely to one generation the presence of the degenerative heredo-familial disease in earlier generations is often betrayed by other signs, especially by the occurrence of cataract in the generation to which the parents of the dystrophic patients belong, and in the members of still earlier generations as well. In addition to cataract, Fleischer found in his families frequent celebacy, many childless marriages, numerous twin births, a high infantile mortality, a very high birth-rate in early generations, with a low birth-rate in later generations, a dying out of certain branches of the families, a steady decline in the family fortunes from comparative affluence to poverty, all of which he regards as evidence that these families are in the grip of a progressive degenerative disease. He points out further that the criteria for the heredo-familial degenerative diseases, as laid down by Londe, Jendrassik, Higier and Bing, are

all fulfilled in that: (1) several members of the same generation are attacked in the same manner (homologous heredity); (2) the disease appears in several members of the same generation at about the same age (homochronous heredity); (3) the basis of the disease is endogenous; (4) the disease progresses steadily from the moment of its appearance. Further, the progressivity in succeeding generations that is seen in other hereditary diseases shows itself in dystrophia myotonica by the occurrence of cataract which appears at an earlier age in each succeeding generation.

Thanks then to these valuable observations of Fleischer upon which we have drawn so freely, we may safely conclude that dystrophia myotonica must be included amongst the typical heredo-familial diseases such as spinal and cerebellar heredo-ataxy, familial cerebral diplegia, Huntington's chorea, progressive neural and myopathic muscular atrophy, Thomsen's disease, familial optic atrophy, amaurotic family idiocy, colour blindness, myoclonus and the rest. Within this group of diseases this most recent addition holds a place of peculiar interest because it supplies a link between two apparently unrelated muscular disorders, in that both myotonia with all the characters of the myotonia of Thomsen's disease and muscular atrophy in nature identical with that of the muscular dystrophies, are found in it together; on the other hand it introduces a new kind of hereditary disorder into this group in the form of general trophic and vasomotor disturbances, cataract, and so on. It remains to be seen whether this kind of disturbance occurs in other forms of hereditary nervous disease, and further research will decide whether an understanding of the nature of dystrophia myotonica will throw any light on the pathogenesis of heredo-familial nervous diseases in general.

V.—Pathology.

The study of the pathological anatomy of dystrophia myotonica has confirmed the views already set forth as to the nature of the disease without leading us to any new facts as to its ætiology, or definitely settling many questions which are still under discussion. By far the greatest number of observations has been made on the muscle alone, removed at biopsy, and the variations in the stage of the disease and consequently in the degree of alteration in the muscle examined, has led to some confusion as to the interpretation of the changes which were found.

The first complete post-mortem examination was reported by

Steinert [54] in 1909. He found degeneration of the dorsal columns, and dorsal nerve roots in the lumbar region of the cord, with resultant pallor of the column of Goll in the cervical region. The ventral horn cells and ventral roots were normal. He considered the degeneration of the dorsal columns in his case to be due to the chance association of tabes with the muscular dystrophy. Later post-mortem examinations have confirmed this view. Hoffmann [31] in two post-mortem examinations found no sign of disease in the dorsal columns of the cord. Hitzenberger [28] reported a case in which the only pathological change in the spinal cord was disappearance and atrophy of some of the ventral horn cells, especially those of the ventro-lateral group in the cervical region. Fischer [11] examined another case without finding any evidence of disease in the central nervous system. In Bramwell's [7] case Dawson found nothing abnormal except "marked pigmentation of the anterior horn cells and cells of the posterior root ganglia; and amongst these cells very numerous amyloid bodies."

In our Case 4, as has been stated, the spinal cord showed no pathological alterations. We have therefore records of six post-mortem examinations since that of Steinert, none of which showed degeneration of the dorsal columns. Atrophy and disappearance of those cells of the ventral horns which are connected with the atrophied muscles had previously been described in cases of myopathy by Holmes [32], and it is therefore not surprising that a similar find should have been recorded by Hitzenberger in dystrophia myotonica.

Comparatively little attention seems to have been paid to the *glands of internal secretion* in post-mortem examinations. This is unfortunate, as the assumption that the disease arises from a faulty activity of these glands rests up to the present on a purely clinical foundation. In our case there were changes in the anterior and middle lobes of the pituitary body and in the cortex of the suprarenal gland, of a degree which, while not absolutely pathological, was certainly beyond what is usual. Unfortunately the testicles, the thymus, the thyroid and the parathyroid glands were not examined microscopically, as at the time of the post-mortem examination our attention had not been drawn to Naegeli's view of the disease.

The changes in the muscles have been particularly investigated by Martin Heidenhain [26] and by Slauck [53]. The former observer constantly found in cross sections of the muscle a few muscle fibres presenting a narrow zone of cross striation under the sarcolemma.

Such fibres were found also in myotonia congenita, in myxœdema, and in the eye muscles of the dog. Heidenhain considered that the appearance was due to one or more muscle fibrils being coiled round the bundle of fibrils which forms a muscle fibre, and on this he based an ingenious theory of the myotonic phenomenon. But the sparseness of fibres showing this change, and their occurrence in other conditions than myotonia, militate strongly against any such view.

Slauck, while confirming in his earlier work the observations of Heidenhain as to the appearance of the muscle fibres, does not consider that they have any relationship with the myotonic phenomenon; and in his more recent work he states that in several cases of dystrophia myotonica he has failed to find any such fibres. In each of our cases we have searched carefully for the appearance described by Heidenhain without finding a single fibre which answered to his description.

The degree of change in the histological appearance of the muscles in dystrophia myotonica appears to vary with the severity of the wasting, and to have little or no relationship with the myotonic phenomena. Thus M. J. Stewart in his examination of the myotonic muscles in Griffith's case found only very slight alterations. Through his kindness we have recently had the opportunity of comparing sections of these muscles with those removed in our Cases 1 and 2. We were thus able to see in muscles which were removed during life, and which showed the myotonic reaction in a typical form, three stages of the disease process. In Griffith's case the muscles were approximately normal, showing only an excess of sarcolemma nuclei which have very little tendency to invade the muscle fibres. In Case 2 the sarcolemma nuclei were considerably more numerous, and many had invaded the muscle fibres, producing chains of central nuclei. In Case 1 a much more advanced stage of the process was seen. The muscle fibres varied greatly in thickness; the contour of some was irregular and a few showed signs of longitudinal division. The longitudinal striation was exaggerated and the transverse striation less definite than normal, so that it was impossible to say which of the two was the more obvious; and in cross sections the individual muscle fibrils could be clearly distinguished. The sarcolemma nuclei had proliferated enormously, giving rise to dense chains of nuclei both within and along the border of the muscle fibres, and many heaps of similar nuclei lay between the muscle fibres. There was, however, little evidence of disappearance of muscle fibres. The intramuscular connective tissue showed only a slight increase.

In our post-mortem case still greater variations were found between different muscles. Some appeared to be unaffected. Others showed slighter or greater changes of the types just described, while from some the muscular substance had almost completely disappeared, and had been replaced by connective tissue; when this was the case the few remaining muscle fibres retained their cross striation, and presented a comparatively healthy appearance, although they were thinner than normal, and contained many central nuclei.

Slauck [53] in his recent paper has given an excellent description of these changes and their gradations, as shown by the muscles removed by biopsy in six cases of the disease. He considers that while they have a remarkable similarity to the changes found in Erb's classic type of muscular dystrophy, there is, in dystrophia myotonica, a greater tendency to the formation of chains of nuclei within the muscle fibres.

This phenomenon was so striking in many of the muscles which we examined that we have felt justified in considering it as *the characteristic* feature of the muscular atrophy. It is true that in its slighter degrees it is present in many forms of muscular wasting. For example it is not uncommon to find in atrophied muscles chains of elongated nuclei lying end to end, and separated by a slight interval. But the occurrence of twenty or more rounded nuclei touching one another and forming a chain down the centre of the fibre is much less common; and we have never seen in any other form of muscular atrophy the numerous solid rods of nuclear matter running down the centre of the muscle fibre, which formed such a prominent histological feature of our cases.

On the other hand, all the muscles examined in Case 4 did not show these central chains or rods, and in the most atrophied muscles, such as the sternomastoids and the anterior tibial group, they were uncommon. They appear, therefore, to be characteristic especially of the early and middle stages of the atrophic process.

The other histological changes in the muscle which occur both in dystrophia myotonica and in other forms of muscular dystrophy have been well summarized by Slauck. As described by him the disease process affects the whole muscle substance, but picks out certain fibres especially, so that thick and thin fibres are seen lying together. In the earliest stages there is an increase of sarcolemma nuclei round thick and thin fibres alike, though in some fibres the atrophic process does not appear to be accompanied by any increase of sarcolemma nuclei. At a later stage, more definite signs of degeneration appear; the sarcolemma nuclei tend to pass into the centre of the muscle fibre, and become

arranged in rows both inside it and along its surface. The muscle fibres lose their polygonal shape and become rounded, and in many of them the muscle substance disintegrates so that only a collection of sarcolemma nuclei remains to mark the place from which a fibre has disappeared. This final disintegration may affect fibres of varying calibre, and not those of the smallest size only. It is usually preceded by an increase of the internal nuclei. These next become surrounded by clear haloes, so that they appear to be nuclei of cells which have invaded the muscle, rather than sarcolemma nuclei. The disintegration of the muscle substance then commences, starting usually in the periphery of the fibres, and soon results in a shrunken muscle fibre crowded with darkly staining nuclei. Along with the degeneration of the muscle fibres there is an increase of the connective tissue between them in which a varying degree of fat deposition takes place, and eventually this fatty connective tissue more or less completely replaces the atrophied muscle. Very frequently in the later stages of the process dichotomous branching of the remaining muscle fibres can be seen. This, according to Slauck, is an ineffective attempt by the healthier fibres to repair the ravages caused by the disease.

Our own observations of the muscles both in myopathy and in dystrophia myotonica agree in the main with this description. In the latter disease we have noticed that the number of internal nuclei is by no means always proportionate to the increase of the sarcolemma nuclei, nor to the degree of disappearance of muscle fibres. Thus in Case 4 the peronei and the long flexors of the forearm showed the greatest number in internal nuclei, but in the peronei there was little if any excess of sarcolemma nuclei on the surface of the fibres; and neither of these muscles gave evidence of much loss of muscle fibres.

The increase of the longitudinal striation was very striking in several muscles in our series, both in those removed during life and in those of our post-mortem case. It was always associated with a diminution in the intensity, and sometimes with complete disappearance, of the transverse striation. In some muscle fibres both longitudinal and transverse striations had disappeared, so that the muscle took on a hyaline appearance. This, however, was not common; it was remarkable that the transverse striation was often preserved even in the finest fibres. In this particular, as well as in the mode of disappearance of muscle fibres, dystrophia myotonica corresponds with the muscular dystrophies and differs altogether from the muscular atrophies of nervous origin.

In the latter the process appears to consist chiefly in a slow pro-

gressive shrinking of the width of the muscle fibre, associated with some degree of increase of sarcolemma nuclei; the transverse striation is lost comparatively early, so that few fibres of less than 25 μ thickness show any trace of it. The shrinkage continues until the sarcoplasm consists merely of a thin thread uniting the numerous sarcolemma nuclei; at this stage considerable areas of the muscle may show, in transverse section, small rounded fibres of about 10 μ in diameter which are constituted chiefly by a swollen sarcolemma nucleus. In some, at the level of section, the whole width of the fibre is taken up by the nucleus, so that it is not easy to distinguish them from mononuclear cells. Nothing resembling this picture is ever seen in dystrophia myotonica. Where a fibre has recently disappeared its place is marked not by one, but by many sarcolemma nuclei, and many of the muscle fibres in the neighbourhood are relatively thick. And in the areas of greatest atrophy the few muscle fibres remaining may still show their transverse striation.

It is more difficult to compare the increase of connective tissue in the two forms of muscular wasting, as we have never had an opportunity of examining a muscle from which the nerve supply has been cut off for more than three or four years. Such muscles show a considerable increase of connective tissue, especially around the muscle bundles, but also between the muscle fibres. In Case 1 of our series of dystrophia myotonica the disease had progressed for rather longer than this without producing more than a slight excess of connective tissue. In Case 4, on the other hand, where the disease had been in evidence for over fifteen years, the fibrosis in the most wasted muscles was extreme; but in other muscles, such as the long flexors of the forearm and the peroneal group which were among those affected at an early stage, there was comparatively little excess of connective tissue.

It appears, therefore, that both in the muscular atrophy following loss of nerve supply, and in dystrophia myotonica, the overgrowth of connective tissue is a purely secondary process, and is largely proportional to the degree of atrophy of the muscles.

VI.—Conclusion.

Dystrophia myotonica is a disease *sui generis* within the group of heredo-familial degenerative disorders. It forms a link between other well-known members of this group in that two of its cardinal symptoms —myotonia and muscular atrophy—are identical in nature with the same symptoms in Thomsen's disease and the familial muscular dys-

trophies respectively. At the same time it introduces a new kind of disorder into this group of diseases, in the form of certain degenerative phenomena in parts outside the muscular and nervous systems.

The fully developed disease is confined in the main to one generation —the dystrophic generation as we have called it—where it occurs in some members of a number of families of the same child-rank in relation to a common ancestor.

The members of preceding generations do not suffer as a rule from myotonia or muscular atrophy, but they often develop cataract which appears at an earlier age in succeeding generations, and genealogical investigations reveal evidence of progressive deterioration in some branches of the stock.

In the dystrophic generation itself some members remain healthy, some may have cataract alone, some may suffer from the disease in an incomplete form—one of the cardinal symptoms, say muscular atrophy, being absent; whilst others present the combination of muscular atrophy and myotonia with certain extramuscular symptoms for which the name dystrophia myotonica has hitherto been reserved. As we have seen in the preceding pages, a majority of the latter conform to the classical descriptions of Batten, Steinert, and Curschmann, but a consideration of the foregoing statements shows that these descriptions apply to a type only—to a syndrome which is merely one aspect of an heredo-familial disease with diverse manifestations.

The disease in all its aspects then remains undesignated, but this discrepancy will be removed if the name dystrophia myotonica is transferred to the disease itself from the syndrome to which it is at present applied. For the syndrome, which also requires a distinctive appellation, "dystrophia myotonica, type Batten-Steinert-Curschmann," would suffice.

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IRON IN THE BRAIN.

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THE specific reactions of different parts of the nervous system to disease are well known to the neuropathologist. He is familiar with the varying forms of neuritis due to alcohol, lead, arsenic, and the toxins of diphtheria; the almost exclusive affection of the motor grey matter of the cord in Heine-Medin's disease, and the local predilections of the morbid processes in the brain in general paralysis and in the atrophies of Pick. Though these specificities are not absolute, they enable the clinician to recognize by means of special symptoms the cause of the disease, even when he cannot determine exactly the parts affected.

A reaction which demonstrates specific chemical properties of some centres of the brain cannot fail to be of interest to the pathologist. The iron reaction does so with wonderful clearness. That this reaction reveals the existence of iron particularly in the nuclei of the extra-pyramidal motor system, which owing to the researches of Wilson and the Vogts are of particular interest at present, is another stimulus for the neurologist to study it.

These centres perhaps more than any others in the nervous system show the existence of a striking specificity to disease. I may only refer to Wilson's disease and Westphal's pseudosclerosis, in which there is an association of progressive degeneration of the nucleus lentiformis and of the liver; the lesions of paralysis agitans localized in the globus pallidus and substantia nigra; post-encephalitic Parkinsonism with characteristic alterations in the substantia nigra; the affection of the globus pallidus, and in some cases of certain parts of it only, in poisoning by carbonic monoxide, manganese, hydrocyanic acid and after strangulation; the diseases of the putamen described by the Vogts as "status marmoratus" and "status dysmyelinisatus," and the "Kernicterus" of Schmorl.

The iron reaction has the great advantage that it is easily carried out and can be consequently applied to a large amount of material with little expenditure of time. The method which I have adopted in the following research has been developed by Spatz, who has published his

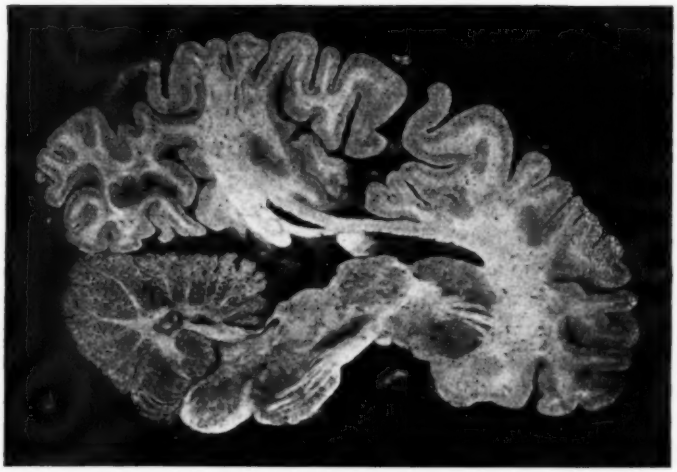

FIG. 1.—Section of a brain which had been fixed for some days in formalin.

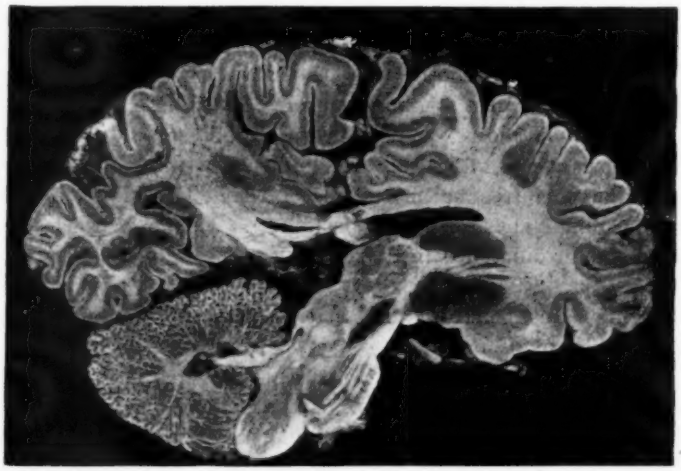

FIG. 2.—The same section as in fig. 1, after being immersed for five minutes in hydrosulphide of ammonium. The substantia nigra and globus pallidus are darkened, and there is a distinct reaction in the nucleus dentatus. The putamen, nucleus caudatus and the lowest layers of the cortex are only slightly darker than before. There is no reaction in the medulla or pons.

own results and brought together the literature on the subject in a recent article [5].

The existence of iron in the nervous system can be demonstrated in either the fresh or fixed state, and macroscopically or microscopically. None of these methods can be neglected, but the most striking results are obtained by examining the fresh brain macroscopically.

A section of the brain is placed in a concentrated deep yellow solution of ammonium hydrosulphide. After some seconds the globus pallidus and the substantia nigra always show a greenish grey colour. It is important to observe the beginning and the order of succession of the colouration, since when they are completed the difference in intensity is not so clear as at first.

After some minutes, when these centres have become dark, other parts begin to react; of these the nucleus ruber shows the strongest reaction, and next the nucleus dentatus cerebelli, the corpus Luysi, the putamen and nucleus caudatus. The difference in the staining of the putamen and of the globus pallidus is of great importance; it is seen most clearly at the beginning of the reaction, but in estimating this difference it must not be forgotten that the putamen has naturally a darker colour (figs. 1, 2, 3). This histo-chemical difference between the globus pallidus and the putamen and nucleus caudatus may be associated with their different ontogenesis and phylogenesis, and with their specific vulnerability; this is seen not only in the rather rare diseases of the extrapyramidal motor centres, for the majority of cases of general paralysis show it with a striking clearness, even those in which during life extrapyramidal motor symptoms were not observed. In the putamen and nucleus caudatus typical cellular infiltrations are found, whilst the globus pallidus is free or nearly free of them, the lamina medullaris externa forming a sharp demarcation (fig. 4). L. Bouman has demonstrated a similar difference in the local distribution of plaques in senile dementia.

In some cases I have found that the nucleus dentatus cerebelli reacted more strongly in its dorsal part. Brouwer [2] has described a case of hemiatrophia cerebelli in which this part was less affected; and from the figure of his paper it seems that in one of Hunt's cases of cerebellar myoclonic dyssynergia [4] this part of the nucleus dentatus was more severely involved. Pathology therefore points out a differentiation in the nucleus dentatus.

Some time after the reaction of the centres of the second group is completed those of the third begin to stain: viz., the corpus mamillare,

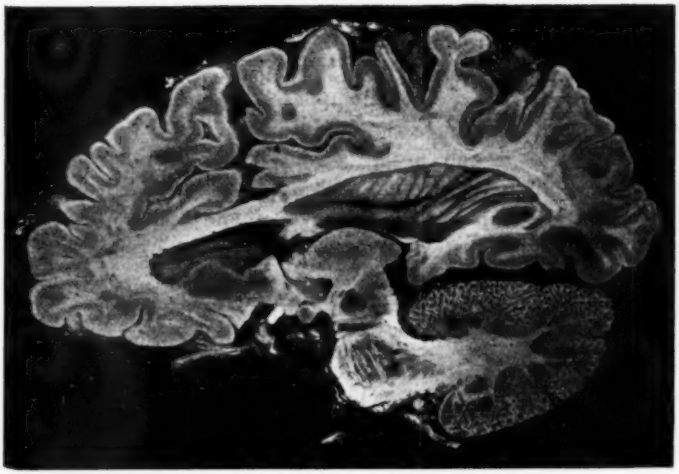

FIG. 3.—The other side of the section in which the nucleus ruber, corpus Luysi and corpus mamillare have taken in the colour.

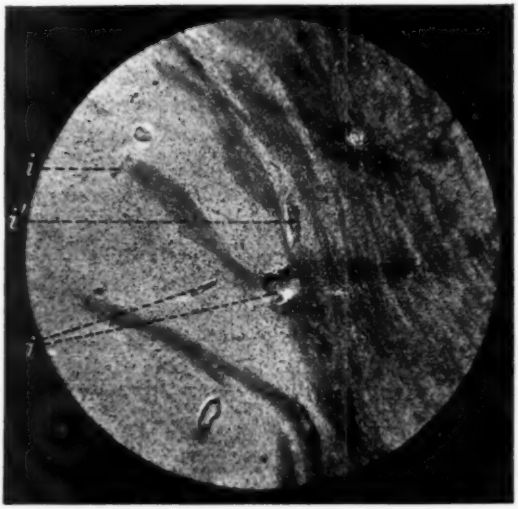

FIG 4.—Putamen and globus pallidus in a case of general paralysis. There are many patches of infiltration in the putamen (*i*) and in the lamina medullaris externæ, but none in the globus pallidus which is in the right half of the figure.

the ganglion habenulæ, the nucleus anterior thalami, the cortex cerebri and the cortex cerebelli. The deeper layers of the cerebral cortex only react clearly, the superficial stain very feebly. The cornu Ammonis often gives a stronger reaction than other parts of the cortex. Perhaps the difference in the reaction of the upper and lower layers of the cortex is connected with its differentiation into two functional regions horizontally spread over the brain, as has been demonstrated by the experiments of Nissl and Winkler, and the researches of Nieuwenhuijse, Bielschowsky, and Van't Hoog, all of which show that the lower layers are in more direct connection with other parts of the brain than are the superficial layers.

A fourth group of centres which do not react at all, or very doubtfully, includes the grey matter of the cord and medulla oblongata, the corpora geniculata, the spinal and sympathetic ganglia, and, what is very remarkable, the inferior olives despite their great resemblance in structure to the strongly reacting dentate nucleus of the cerebellum.

The centres giving the strongest reaction, as the globus pallidus, zona reticularis of the substantia nigra, nucleus ruber, corpus Luysi and nucleus dentatus, have in the fresh state a light reddish brown colour. This cannot be explained simply by the existence of iron in these centres, for Spatz has shown that the principal reaction is given by colourless iron combinations; there are centres of similar colour, as the corpora geniculata, in which iron is not found. Though it is not yet possible to explain it, the fact may be of significance.

The reaction can be also obtained in macroscopical and microscopical sections by the Berlin-blue test. This test has the advantage that the staining does not develop so rapidly, and the order of beginning and the distinction between the centres can be therefore followed more easily; but it possesses the disadvantage that the fluids themselves produce some colouration. The method is very simple: a section of the brain is placed for a quarter of an hour into a freshly made $2\frac{1}{2}$ per cent. solution of ferrocyanide of potassium, and then in an abundant quantity of 1 per cent. hydrochloric acid. It is not advisable to leave the section longer than a quarter of an hour in the acid, since spontaneous staining may occur.

Fixation for one or two days in formalin does not produce marked differences, but very old formalin material cannot be used, since the formalin dissolves out the iron. Old alcohol material, however, may be employed, but the white fibres of the reacting centres, which take no colour in the fresh material, stain intensely after fixation in alcohol.

It is not strictly necessary to avoid iron or steel instruments in cutting the material.

The best method for *microscopical examination* is the Turnbull-blue reaction; it is not so satisfactory in thick macroscopical sections because it does not stain deeply enough, but in microscopical sections it gives strongly contrasting colours. The sections remain for twelve to twenty-four hours in a concentrated solution of ammonium hydrosulphide; then they are washed carefully in distilled water, and put into a mixture of 1 per cent. hydrochloric acid and a freshly made solution of 20 per cent. ferricyanide of potassium, in equal quantities; after being washed they may be stained by alum-carmin. As celloidin sections wrinkle very much under the action of ammonium hydrosulphide the celloidin should be dissolved out previously.

All these reactions render visible a part only of the iron, that in certain organic combinations, as in hæmoglobin, not reacting. In order to estimate the total quantity of iron the tissue must be destroyed and examined chemically; our histo-chemical methods show the existence of iron *in situ*, but that part of it only which reacts to these chemical tests.

In microscopical preparations the iron is seen either as: (1) A diffuse reaction of the whole tissue or of some part of it; (2) iron pigment; or (3) small granules. The latter is the most interesting form, because it proves the vital accumulation of the iron in the tissues. The granules which give the reaction have no natural colour, as may be seen in unstained preparations. They are found only in the cytoplasm of ectodermal cells (glial and nervous) of the centres of the first group, and in the putamen and the nucleus caudatus. The melanin cells of the substantia nigra contain no iron granules.

Spatz concluded that the iron demonstrable histochemically in the extra-pyramidal system has nothing to do with the destruction and synthesis of hæmoglobin; it is not increased in cases of hæmorrhages or in intravascular hæmolysis. Its quantity in the brain is very constant, in contradistinction to the liver and spleen in which hæmoglobin is destroyed and reformed.

In the fœtus and new-born child no iron is found in the brain, but the liver and spleen contain it in large amounts. It is the globus pallidus that first gives the reaction; Spatz saw it in a child nearly half a year old. The substantia nigra follows, and then the other centres, corresponding to the intensity of their reaction in the adult. It is not yet

proved that the absence of the reaction in very young children is due to absence of iron in the reacting centres. It may be that in them the iron exists in a histo-chemical form in which it cannot be demonstrated by the tests employed. The brains of some mammalia give the reaction too, though not so intensely, in those portions which correspond to the areas which react most strongly in the human brain, that is the globus pallidus and the substantia nigra. Kappers employed it on the brains of birds and obtained a clear reaction in the meso- and palæo-striatum, the parts homologous to the globus pallidus. It is still more interesting that he obtained a reaction too in the nucleus rotundus, a mass of grey matter the significance of which is doubtful, though it is regarded by him as the analogue, if not the homologue, of the corpus Luysi in man which gives a distinct iron reaction.

The iron reaction gives very interesting results in the brain of patients who suffered from general paralysis. Bonfiglio [1] was the first who demonstrated that the yellow pigment found in the adventitial spaces of the vessels in this disease contains iron. Lubarsch found iron pigment without exception in more than a hundred cases of general paralysis.

The method of examination is very simple: a small piece of the cerebral cortex placed in ammonium hydrosulphide shows after some minutes characteristic dark spots and stripes in connection with the vessels, while a piece of a non-paralytic brain put into the same fluid shows only a feeble staining in the lower layers of the cortex. A small piece of the paralytic cortex, as large as a pin's head, laid on slide, rubbed with glycerine under a cover-glass and examined with the microscope, shows very characteristic deep black coloured spots along the vessels (fig. 5). This iron is hæmatogenous. Spatz found it in mesodermic granular cells, in adventitial and endothelial elements, and in Nissl's "Stäbchenzellen." These iron granules never exist in glial cells, nor in the nervous cells of the cortex.

Lubarsch found this pigment in his hundred cases of general paralysis only, and Spatz detected it in all his cases of general paralysis and in three cases of trypanosomiasis, a disease which according to Spielmeyer is closely related to general paralysis, but in no other affections of the brain. I have also found the reaction always positive in general paralysis, even in a brain which had remained for some months in formalin. As the whole test takes a few minutes only to carry out we have in it a rapid means of diagnosis of general paralysis; it may be also used as a help in

the diagnosis of pieces obtained by puncture or operation on the brain.

Hallervorden and Spatz [3] have described interesting results from the application of the iron reaction to the brain of a patient with extrapyramidal motor symptoms. There was an almost exclusive affection of the globus pallidus and the substantia nigra, which in the unstained state were of a red-brown colour. The tests demonstrated here, and here only, an abundance of iron. In the majority of cases of disease of these centres, however, Spatz has not found an increase of iron.

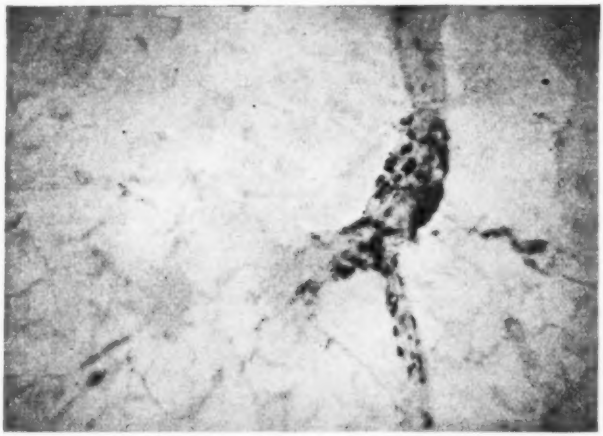

FIG. 5.—Iron reaction around a vessel in the brain of a general paralytic.

I observed in the asylum of Santpoort a young woman who suffered for some years from marked extrapyramidal motor symptoms. The globus pallidus, the putamen and nucleus caudatus were reddish-brown, especially the globus pallidus, and the iron reactions revealed a considerable increase of iron in them.

It is not my aim to give here a complete report of the results obtained by the iron reaction in the brain. I desire only to direct attention to the importance of this promising method of research, which is extremely simple and falls within the reach of every pathologist.

We do not yet know the meaning of the chemical differences demonstrated by the iron reactions, but it is of importance, especially

since its investigation may lead to the discovery of other reactions which may demonstrate chemical peculiarities in centres which are the substrate of specific energies and their psychical equivalents. Theories are easily to be made, but it is a good rule, often neglected in medicine, to follow the maxim of Hughlings Jackson, that "the study of things caused must precede the study of causes of things."

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[3] Hallervorden and Spatz. *Zeitschr. f. d. gesamte Neurol. u. Psychiatr.*, 1922, **79**, 254.
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Proceedings of the Section of Neurology of the Royal Society of Medicine.

President—Dr. Wilfred Harris.

Meeting held December 14, 1922.

Dystrophia Myotonica.

Dr. W. J. Adie read a paper on Dystrophia Myotonica (see p. 73).

Dr. James Taylor dealt chiefly with the familial relations of these and similar diseases. He referred to the fact that in the muscular dystrophies, Friedreich's disease, Leber's optic atrophy and other hereditary affections, there were frequently large families, especially in the affected generations; but in many of these families the mortality rate in early life is high. This seemed to him the reason why the diseases tend to die out. He also discussed the relation of the disease to the myopathies, which seemed to him to be a close one. He had seen one case of pseudo-hypotrophic myopathy in which there existed cataract similar to those found in dystrophia myotonica.

Mr. Leslie Paton said that it was not yet possible to formulate a clear idea of the nature of the cataract which occurred in this disease. It seemed to be a posterior cortical cataract, the type found in retinitis pigmentosa and in other choroidal and retinal diseases. In a recent case he had found only a ring of granular opacities in the periphery of the lens, and peripheral striæ such as occur in senile cataract.

Sir John Parsons pointed out that the term posterior polar cataract was not an exact description; that it should be posterior cortical. This is the type of cataract which is often associated with, or results from, a general toxæmia.

Dr. Walshe referred to a case recently under his care in which the characteristic symptoms of dystrophia myotonica were associated with other anomalous symptoms, as minor epilepsy, abductor palsy of the vocal cords, complete foot-drop, though there was very little atrophy of the muscles of the legs, and Romberg's sign. Despite the latter the sense of position and the appreciation of vibration in the legs were good.

Dr. GREENFIELD referred to the fact that in one member of the family under his care there was degeneration of the membrane of Bruch; in another case the cataract was unilateral.

Dr. HARRIS dealt with the psychical changes which are prominent in many cases of this disease, and pointed out that similar abnormalities were found in other hereditary and familial affections.

Dr. ADIE in reply said that the further study of these families brought out many interesting features. The affected families seemed to sink lower and lower in the social scale. Many dystrophic patients have had children who have been mentally defective, while others who have married have been childless. He agreed with Dr. Taylor's remarks that in the earlier generations large families were common, but the infant mortality was high. He agreed too that the term posterior polar cataract is inexact. Romberg's sign has been observed by others, as by Curschman, and in one case at least autopsy has revealed degeneration of the dorsal columns of the cord.

Meeting held March 8, 1923.

The Treatment of Neuro-Syphilis.

Dr. FARQUHAR BUZZARD said that certain principles should determine the treatment of syphilis of the nervous system. In the first place, that no distinction should be drawn between the treatment of the interstitial and parenchymatous forms of neuro-syphilis; in the second, we are justified in speaking of the cure of neuro-syphilis only when the complete eradication of the spirochæte or the continued abeyance of its activities is attained; finally, since we can never assure the patient that he is cured of the syphilitic infection, it is our duty to advise all patients who have been infected to continue intermittent treatment for the rest of their lives.

The gradual accumulation of clinical experience has shown that a negative Wassermann reaction is certainly not evidence of cure, and the fact that it has been regarded as such has made it an obstacle in the way of efficient treatment, since a negative reaction gives rise to delusions of security which often lead to the suspension of the periodic courses of treatment year after year which can alone prevent the development of neuro-syphilis or a recurrence of its symptoms. He is convinced that the view until lately held that, though meningeal and vascular lesions

respond to anti-syphilitic measures, no benefit can be expected from the similar treatment of tabes and general paralysis is a mistaken one, since in both of these conditions, and especially in tabes, early diagnosis and continuous treatment are often attended by satisfactory results, though it may not be possible to abolish the symptoms of this disease already present.

The relative efficiency of various methods of treatment is still a matter of controversy. Personally, he is in the habit of using both mercury and arsenical compounds and continuing their administration periodically regardless of the results of serological laboratory tests. The only contra-indications for the use of intravenous injections of arsenic are advanced cardio-vascular changes and renal inefficiency.

Dr. HENRY MACCORMAC entered the discussion as a syphilologist rather than as a neurologist. In the study of syphilis, attention may be focused on either the signs and symptoms and the effect of treatment on them, or on the state of certain biological reactions such as the Wassermann test. These two methods are complementary, but the latter is the more important, since it is only when the biological reactions become negative that we are entitled to assume that the cure has been effective. In early syphilis it is possible not only to remove the symptoms but also to obtain a normal Wassermann reaction, but it is much more difficult to influence either the symptoms or the reactions in the later stages of the disease. He spoke of the disease being cured in its early stage when the Wassermann reaction was found to be persistently negative after a prolonged course of treatment. In the later stages the greatest benefit is obtained by a short intensive course of medication, as ten intravenous injections of salvarsan followed by twelve mercurial injections. There is an intermediate class of case in which the patients respond insufficiently to early treatment and their blood and cerebrospinal fluid give positive reactions; in these, too, there is a possibility of permanent cure by prolonged treatment.

In his opinion the existence of a neurotropic spirochæte is not yet established, and consequently there is no argument in favour of special forms of treatment in neuro-syphilis. Further, the changes found in cerebrospinal fluid in the early stages of the disease do not, in his opinion, indicate an actual involvement of the central nervous system, since the proportion of syphilitics who develop nervous manifestations is very much smaller than the proportion in whom such changes are found in the fluid. It may, however, be that in its early stage syphilis of the nervous system is curable by remedies introduced into the blood.

The treatment of neuro-syphilis is complicated by the physiological peculiarities of the cerebrospinal fluid and the difficulties of influencing it by intravenous medication, but as there is evidence that it is possible to do so in the earlier stages of infection, some beneficial effect, at least, may be expected from adequate treatment in the chronic stages of the disease. He expressed doubt as to the efficacy of spinal drainage and of intrathecal injections.

Dr. HENRY HEAD pointed out the difficulty in distinguishing, either by clinical symptoms or by laboratory methods, certain cases of cerebro-spinal syphilis from general paralysis. The failure to recognize this difficulty had undoubtedly led to loose statements and very unreliable statistics, since one condition was more or less curable and the other was little if at all influenced by treatment.

Dr. RIDDOCH insisted that laboratory tests and clinical symptoms should be used in conjunction in determining the form of treatment required and its duration. In his opinion there could be no doubt that a positive Wassermann reaction indicated the activity of syphilitic processes which consequently demanded urgent treatment.

COLONEL HARRISON emphasized the fact that a negative Wassermann reaction does not mean the cure of syphilis. In his experience even general paralysis could be favourably influenced by sufficiently intensive anti-syphilitic treatment. He believed that the most important step in the prophylaxis of neuro-syphilis was the examination of the cerebrospinal fluid some time, as five years, after the original infection. He had never found fluid that was negative at this period become positive subsequently. He could not accept the hypothesis of the duality of the *Spirochæta pallida*, since all evidence at his disposal pointed to the contrary. He believed too that Dr. MacCormac was wrong in suggesting that it is chiefly on mercury that reliance should be placed in treatment in the later stages of syphilis; it seemed to him more rational that all methods at our disposal should be adopted. He had seen some good results from intrathecal injections when the intravenous method had apparently produced very little effect.

Sir JAMES PURVES-STEWART thought it a mistake that any routine of sterotyped treatment should be adopted, as each case of neuro-syphilis demanded individual attention. It seemed to him that no drug or mode of treatment should be adopted exclusively, as each is supplementary to the others. He referred particularly to the intracisternal treatment of general paralysis. It consisted of the injection of salvarsanized serum into the cisterna magna, the beneficial action being probably due, not to

the infinitesmal amount of salvarsan the injected substance contained, but to the antibodies evoked in the serum of the patient. Substances injected into the cisterna magna circulated slowly, some passing down the spinal canal, but the greater part forwards into the basilar and interpeduncular cisterns, and thence over the whole cortex, being ultimately reabsorbed by the cortical capillaries. He described the technique of the operation and pointed out that it involved very little risk. He recorded a series of cases in which under this form of treatment more or less dramatic improvement had taken place in the clinical symptoms and a fall in the number of cells in the cerebrospinal fluid, though he had to admit that he had never seen a case in which the Wassermann reaction had been made negative in general paralysis by this or any other method of treatment.

Dr. SYMONDS stated that in his experience there was very little risk in using large doses of arsenical compounds in neuro-syphilis, since they are on the whole better tolerated in these cases than by patients suffering from the primary disease. He formerly commenced by injections of 0·6 gramme of salvarsan and then proceeded to 0·9 gramme, continuing until the patient had taken 10 grammes in the first course. By this form of treatment, however, he had had several cases of jaundice and exfoliative dermatitis, and consequently he now divided the course into two, with six weeks interval between them. He also agreed that a negative Wassermann reaction might be found in both the blood and cerebrospinal fluid in progressive cases of tabes. He had at present a man under his care in whom the symptoms are increasing though the reaction is negative in both the blood and cerebrospinal fluid, but his wife's blood gives a strongly positive reaction.

Dr. FEILING spoke of the frequency of a negative Wassermann reaction in the blood and normal cerebrospinal fluid in cases of undoubted syphilis of the central nervous system. He referred to one case of syphilitic meningo-myelitis in which the Wassermann reaction was positive eight years ago but had become negative under treatment although the symptoms had progressed steadily.

Dr. HARRIS insisted that it was on the clinical rather than by biological or chemical reactions that all cases of syphilis of the nervous system should be treated. In his experience the original salvarsan or its substitute kharsivan is much more efficient than either novarsenobillon or galyl. He referred to some cases in which salvarsan had produced much improvement after these other remedies had been tried without success. He had had a considerable amount of experience in

Notices of Recent Publications.

Lehrbuch der Nervenkrankheiten. Von H. Oppenheim. 7te wesentlich vermehrte und verbesserte Auflage. Erster Band. S. 923, mit 323 Abbildungen im Text und 11 Tafeln. Berlin: S. Karger. 1923. Price 27 Marks.

Oppenheim's textbook has for so many years enjoyed an assured international position that the simple notice of a new edition would suffice, were it not that his death has thrown the duty of its preparation into other hands. The responsibility has fallen mainly on the late author's assistant, Cassirer, but he has happily invoked the help of Goldstein, Nonne and Pfeifer, each of whom has undertaken the revision of the subjects with which he can deal with authority.

The aim of the editors has been to alter as little as possible, and the chief changes we find are, therefore, additions made necessary by knowledge acquired during the past ten years, and especially by experiences arising from the late war.

The first volume (which is alone under notice here) has been, as compared with that of the fifth edition, increased by 230 pages, and contains 70 additional illustrations. A large part of this increase is due to a fuller description of the lesions of the peripheral nerves, and to a more complete discussion of the morbid anatomy and pathology of the diseases of the spinal cord.

The bibliographic references, which are still given in footnotes, have been kept up to date, and consequently make this edition even more useful for the purpose of reference. There can be no doubt that, under its new editors, Oppenheim's volumes will remain the most complete and reliable textbook on the subjects with which they deal.

Dementia Præcox, intermediäre psychische Schicht und Kleinhirn-Basalganglien-Stirnhirnsysteme. Von Dr. Max Loewy. Abhandlungen aus der Neurologie, Psychiatrie und ihren Grenzgebieten. Heft 20. Berlin: S. Karger. 1923.

In this work an attempt is made to explain the manifestations of dementia præcox on an anatomical basis.

It is assumed that there exists in man an intermediate psychic layer which corresponds with the cerebellar-basal ganglia-frontal lobe system described by

intrathecal therapy. He always waited a fortnight after an intravenous injection of salvarsan before withdrawing a patient's blood. This method had been particularly useful in tabes; though the injections generally produced intense pain for a few hours, the tabetic pains frequently disappeared for a time after each injection. He had seen no good result from intrathecal use of salvarsan in general paralysis.

Dr. BUZZARD in reply said that he could not agree with Dr. MacCormac's observations, which seemed to be mainly based on the Wassermann reaction.

In his introductory remarks he had not laid down any special routine treatment, since each patient suffering with syphilis of the nervous system required individual attention and continuous treatment, no matter what clinical form the disease assumed. He had not been convinced that the cisternal injections employed by Sir James Purves-Stewart were of any advantage, and the cases he cited did not show that it was more successful than intramuscular or intravenous injections.

Dr. MACCORMAC said that dermatitis or jaundice as a sequel to arsenical injections should be very rare, provided that this remedy was properly and intelligently employed.

to deliver" and in writing it around "some pervasive idea, some ideal," in other words, in presenting in it any views or hypotheses which they consider may explain the working of the nervous system and the morbid phenomena of its diseases.

If, on the other hand, the book is meant to be a guide to the student whose knowledge is rudimentary, and whose critical faculties have not been developed by practical experience with disease, hypotheses, which are merely guesses at truth and unsupported by facts and tangible arguments, should not occupy the prominent place they do in this volume. There seems, for instance, little justification for the attempt to explain so much as the authors do by primary lesions of the autonomic nervous system and disturbances of the endocrine glands; no serious argument exists in favour of the assumption that the lesions of disseminated sclerosis may be due to the vegetative control metabolism of the spinal cord being at fault, or that myasthenia gravis is the result of a disturbance in the muscle vegetative mechanisms, or that a faulty emotional control plays a part in the pathogenesis of diabetes, or that gastric and duodenal ulcers result from increased adrenalin activities excited by the emotions of fear and hate. Such statements, unsupported by reliable clinical or experimental evidence, not only make many paragraphs of the book ridiculous, but are liable to mislead the student and do serious harm to the scientific study of medicine. In other places, as in the discussion on the mode of working of the sympathetic system, all physiological evidence is thrown overboard and is replaced by "ideas" which are more easily assimilated with the authors' creeds.

It is regrettable that these features diminish so seriously the value of a book that would be otherwise useful and fill a distinct gap. The descriptions and discussions of most diseases are clear, concise, and written with a thorough knowledge of the subjects. Diagnosis and treatment receive as a rule adequate attention, and the sections on pathology and morbid anatomy are usually sufficient for a volume of its size. Here and there there are lapses and inequalities; the chapter on aphasia, for example, is unsatisfactory and incomplete.

The section on psychiatry is perhaps the best part of the book. The attitude of the authors to the histological lesions recently discovered in dementia præcox is interesting and on the whole commendable.

This edition has been largely re-written and carefully revised, and it consequently exceeds its predecessors in size. The illustrations, for the most part taken from other books and monographs, have been carefully chosen, and are one of the best features of the volume.

Problems in Dynamic Psychology. A Critique of Psycho-analysis and suggested Formulations. By JOHN T. MACCURDY. Pp. 377. Cambridge University Press. 1923. Price 12s. 6d.

The first half or more of this book is devoted chiefly to a destructive criticism of what the author regards as the inaccuracies and inconsistencies of Freud's doctrines. If makes dreary, barren reading. We follow the author

Kleist. The various centres of this system may be disturbed separately or in various combinations, both by organic lesions and in dementia præcox.

Organic lesions of the cerebellum-basal ganglia-frontal lobe system give rise to symptoms resembling those of dementia præcox, and, therefore, reasoning by analogy, it is assumed that this mental disease depends on some disturbance of this system.

The dominating characteristic of dementia præcox is described as disturbance of movement, e.g., difficulty in general movements and in movements of expression, compulsion movements, and psycho-motor reactions. Lesions of these parts have not been demonstrated in dementia præcox, and though demonstration might not be easy even if they existed, some reserve is necessary before attributing by analogy the psycho-motor alterations in dementia præcox to local changes in the basal ganglia. The multiformity of the symptoms in the disease is another difficulty, which is overcome by assuming that lesions in the various parts of the system may explain the differing syndromes, and the extent, course, direction, spread, severity and chronicity of the disease.

The similarity between some cases of dementia præcox and manic-depressive psychosis on the one hand, and hysteria on the other, is referred to; it is assumed that dementia præcox is due to disturbance of the system as a whole, while in the manic-depressive group the affective systems of the thalamus are affected, and in hysteria perhaps some parts of the basal ganglia.

There are many references to the work of Kleist, but little evidence of the existence of such an intermediate psychic layer is produced in this monograph, and no reason is offered for excluding the participation of the other parts of the nervous system in the pathology of dementia præcox. The possibility, for instance, of different compulsion movements of expression being due to psychic causes is not considered. The hope is expressed that further investigations will allow of more complete differentiation of types of mental illness in dementia præcox, but there is nothing to show how mere symptomatology and differentiation into types will lead to a better understanding of the disease.

Diseases of the Nervous System: A Textbook of Neurology and Psychiatry. By SMITH ELY JELLIFFE and WILLIAM A. WHITE. Fourth Edition, revised, re-written and enlarged. Pp. 1120, with 475 Illustrations and 23 Plates. Philadelphia and New York: Lea and Febiger. 1923. Price 9.50 dollars.

The value of such a book as this must be measured by the purpose for which it is intended or the use to which it is put. Its sub-title, "A Text-book of Neurology and Psychiatry," suggests that it is written for the ordinary student or general physician who wishes to acquire a knowledge of nervous diseases or elucidate some point of immediate difficulty, though the remarks by which it is introduced indicate that in it the authors hope to provide a handbook for the serious student of neurology. If the latter is its intended scope, the authors are certainly justified in using it as a vehicle for a "message

through the maze of Freudian verbiage to come out, for the most part, nowhere. Doubtless there is much truth hidden in the Freudian hypotheses, and a constructive account from the present author of what there is of value in them to psychology would have been welcome.

The second half of the book is more interesting and readable. In it the author deals with the instincts as factors in dynamic psychology. He begins with a chapter on the late Dr. Rivers' book on "Instinct and the Unconscious," which he criticizes adversely. From this he proceeds to the development of a pragmatic conception and classification of instincts, and discusses in detail the value of the ego instincts, the sex and the herd instincts, and the importance of the co-operation and conflicts of the instincts. This constructive part of the book does much to redeem the unsatisfactory, disjointed impression left by the earlier chapters.

L'Encéphalite épidémique, Étude clinique. By LOUIS REYS. Paris: Maloine et Fils. 1922. Price, 8.50 francs.

The study of encephalitis lethargica has recently been stimulated by the appearance of a variety of sequelæ, and a contribution to such a study from the hands of a clinician warrants attention.

After mentioning the symptoms and signs at the onset, the author passes to a detailed description of the various types of the disease to be seen in the early stages. Having devoted many pages to the disorders of the ocular apparatus, he then lays great stress on a labyrinthine type, in which giddiness, vomiting, staggering gait and inco-ordination are prominent features; he describes several cases and claims originality for the recognition of this labyrinthine type. Reference is then made to the myoclonic and choreic types. In a contribution to the Parkinsonian syndrome he alludes to a case of this kind which rapidly developed myositis ossificans in the rigid muscles. An analysis of the effects of the disease on the sympathetic system and on the viscera and endocrine glands follows, with a suggestion that asthenic cases may result from affection in the suprarenals. The psychological aspect of the disease is briefly dismissed with a reference to the works of Truelle and G. Petit.

Following upon a few pages dealing with methods of treatment and their relative value, the author proceeds to attempt to correlate the clinical findings with the anatomy of the central nervous system, basing his views on a theoretical, at times almost hypothetical, foundation.

In discussing the late sequelæ most prominence is given to the Parkinsonian syndrome which is, in his experience, the most frequent type. He records one case which first developed signs three years after the acute attack.

Fault may be found with this volume, in that too great an attempt at classification into types is made, with the result that undue prominence is given to certain of the rarer manifestations of this disease.